FORMULATION AND EVALUATION OF FAST DISINTEGRATING SUBLINGUAL MUCOSAL DELIVERY OF DRUG ZOLMITRIPTAN USED FOR THE TREATMENT OF MIGRAINE

DISSERTATION

Submitted to

The Tamilnadu Dr. M.G.R. Medical University

Chennai – 32

In partial fulfillment for the award of the Degree of

MASTER OF PHARMACY

In the Department of Pharmaceutics

APRIL – 2016

DEPARTMENT OF PHARMACEUTICS

PADMAVATHI COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

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CERTIFICATE

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Constitutes the original work carried out by

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ACKNOWLEDGMENT

"With the blessings of Lord Ganesha"

I humbly owe the completion this dissertation work to the almighty whose love and blessing will be with me very moments of life.

It is a delightful moment for me to put in towards all my deep sense gratitude to my esteemed guide **Mr.A.VASANTHAN, M.Pharam, M.B.A., Assistant Professor Department of Pharmaceutics** of Padmavathi College of Pharmacy and Research Institute, for her unstinted guidance, innovative ideas, constructive criticism constant encouragements and continues supervision and also for making the requisite arrangement to enable to me to complete me dissertation work at Padmavathi College of Pharmacy and Research Institute in Dharmapuri.

I am heartily thankful to **Dr.K.L.Senthil Kumar., M.Pharm., Ph.D., Principal** of Padmavathi College of Pharmacy and Research Institute, Dharmapuri, for his help and motivation to carry out dissertation work in College.

I would like to express our sincere thanks to **Kalvi Kodai Vallal M.G.Sekar., B.A.B.L., Ex.M.P., & M.L.A.,** Chairman of Sapthagiri Padmavathi & Pee Gee Group of institution and industries.

It is with great pleasure and humble thanks to my eminently; esteemed teacher **Mr.A.Vasanthan, M.Pharm., M.B.A., Asst.Professor**, **Mr.Mohanasubramaniam,** M.Pharm, Professor, Department of Pharmaceutics, Padmavathi College of Pharmacy and Research institute, Dharmapuri for his valuable guidance, keen interest, inspiration, unflinching encouragement and moral support throughout my dissertation work.

I am elated to place on record my profound sense of gratitude of, **V.Palanivel,** M.Pharm., **Mr. Paneerselvam**, M.pharm **Mr.Vimalan**, M.Pharm., Department of Pharmacology, **Mr.Raja,** M.Pharm., **Mr.Venkateswaran,** M.Pharm,

Mrs.KartiKayani, M.Pharm., Department of Pharmacognosy, **Dr**. **P.D.Gokulan**, M.pharm., Ph.D, Head, Department of Pharmaceutical Chemistry, **Mr.M.Saravanan,** M.Pharm.,Head, Department of Pharmaceutical Analysis and all of our college teaching and non teaching staff for their valuable suggestion.

Words are not sufficient to express my depressed love and appreciation to my affectionate bellowed parents and my sister who always inspired and cherished me and fill my heart with their love **strength** which makes my project completion successful.

Friendship is a treasured gift and true friends are few. I am lucky to have enough of them like **Satheshkumar** for giving me constant encouragement, moral support and dynamic cooperation throughout my dissertation work.

Finally I consider this is an opportunity to express my gratitude to all the dignitaries, who have been involved directly and or indirectly with the successful completion of this dissertation.

I would like to extend my thanks to non-teaching staff of Padmavathi College of Pharmacy and all those who helped me directly or indirectly at the time of my thesis work. A word of thanks to all those gentle people, who helped directly or indirectly during the time of need.

At last but not least, I would like to thank almighty with whose blessings this work has been completed,

Thanks to one & all

V.LOGANAYAKI

(Reg. No. *261410852*)

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INTRODUCTION

Drug delivery through the oral mucosal membrane is considered as alternative to the oral route. The sublingual region of the oral cavity in the floor of the mouth is far more permeable than the buccal cavity (Leow et al., 1992).The permeability differences are usually based on the comparative thickness, supply of blood and keratinisation of the membranes. Difference in the permeability of the various mucous membranes, affects the amount of drug delivery from the physicochemical properties to be delivered. The sublingual root (Physiological pH 6.5) has the ability for providing a substitute to IV dosing for quick delivery of drugs to the systemic flow. It bypasses gastrointestinal and presystemic metabolism and is a suitable form for delivery of drug relevant in patients with difficulties in swallowing (Kurosaki et al., 1991).

Tablet that are disintegrated/dissolved quickly in patient's mouth are suitable for elderly, patients with swallowing difficulties and children (Fu et al., 2004), and in situations where portable liquids are not obtainable (Allen et al., 2003). The minute volume of saliva is generally enough for disintegration of tablet in the oral tract. The medication is absorbed either partially or entirely into circulation systemically from blood vessels surrounded by the sublingual mucosa or ingested as a solution to be immersed from the GIT. Sublingual route generally provides a quicker onset of action compared to orally taken tablets and the fraction absorbed during the blood vessels of sublingual route bypass the hepatic system. The advantages of fast disintegrating tablets are increasing and being recognised in academics and in industries (Chang et al., 2000). The main approach in developing the fast dissolving tablet is by using super disintegrants like sodium starch glycolate (primogel, explotab), cross linked carboxy methyl cellulose (croscarmellose), crospovidone, polyvinylpyrollidone (polyplasdone) etc and using

highly water soluble excipients (Kucchekar et al., 2003).

This tablet exhibit a quick and impulsive disintegration in the mouth, when contacted with saliva, without alteration from the package; they can be extracted or handled (Schiermeier et al., 2002). The active ingredient can thus quickly dissolve in the saliva and can be absorbed through the membrane it passes, at the time of deglutition, if not sheltered from pre-gastric absorption. (Hisakadzu et al., 2002). To perform these needs, tablet must be extremely permeable, incorporating hydrophilic substances and should have the ability to quickly absorb water for a fast disaggregation of the matrix. Various techniques, like freeze drying, moulding or direct compression are at present engaged for the preparation of the formulations in the present pharmaceutical market. Honda et al (1998) published that a half of the patients experienced trouble in taking medication and felt that tablet was superior and easier compared to other formulations like capsules or powders.

1.1 Characteristics of fast disintegrating systems

1.1.1. Simplicity of administration

Fast disintegrating drug delivery systems are very easy to administer, handle and leads to betterment of patient compliance. Generally, aged people experience a lot of difficulty to swallow the dosage forms like solutions, suspensions, tablets and capsules due to dysphasia and tremors of extremities. This problem can be overcome by using fast dissolving delivery systems.

1.1.2 Medicament taste

Almost all drugs are unpalatable, fast disintegrating drug delivery systems frequently containing a medicament in a taste covered form. These drug delivery systems liquefy in the mouth of the patient and release the active ingredients as soon as they come in contact with the oral cavity. Taste masking of drugs was very important from patient point of view.

1.1.3 Hygroscopicity

Most of the dosage forms that dissolve fastly are very hygroscopic and does not maintain physical integrity at normal conditions such as humidity which requires special product packaging.

1.1.4 Friability

Fast disintegrating tablets should dissolve in mouth which are made up of soft-molded matrices (highly porous) and compressed into tablets using less compression force, making the tablets more friable. It is not easy to handle and requires peel-off blister specialized packaging.

1.1.5 Mouth fee

Feel in the mouth is extremely important and the tablet should give pleasant feel to the patient. After disintegration of tablet, large particles that are not soluble or gradually soluble in saliva may give a disagreeable gritty feeling. It can be solved by keeping most of the particles under the lower size. In some instances, some flavors can enhance an improved perception of feeling in the mouth, ensuing that the product is less gritty, yet there is a change in the flavor.

Effervescent can also be added to get better mouth feel and helps in disintegration and also reducing the dryness of a formulation.

1.2 Advantages of fast dissolving drug delivery through sublingual route

Reduction in the dose there by minimizing the frequency of dosing Heinemann et al, 1976). Convenient for patients who refuse to swallow the tablet, such as children, elderly people, mentally ill, disabled persons, bed ridden patients, renal failure patients, stroke victims and uncooperative patients (Indurwade et al., 2002). Convenient way of management and precise dosing compared to liquids (Bredemberg et al., 2003).

Water is not required to gulp down the dosage form, which is highly suitable for the patients who are travelling and having no access to water (Devarajan et al., 2000).

Good mouths feel of FDTs which helps to change the fundamental bitter view of medication particularly in children. It provides advantages of liquid medication in solid dosage form. Rapid dissolution of drug, which produces fast beginning of action, is absorbed through the oral cavity when the saliva passes downwards to the stomach. In these cases the availability of drugs to the body is enhanced.

Pre-gastric absorption results in increased bioavailability and as a result of reduction in doses, medical performance is improved by reducing the side effects. fter administration, it leaves minimum or no residue in the mouth (Gole et al., 1993).

Conventional low cost packaging and processing equipments are available which are compatible with taste masking having pleasant mouth feel. They also show low sensitivity towards environmental situations such as temperature and humidity (Bhaskaran et al., 2002).

New and in the management of life cycle. Stability for longer time, since the medicine remains in solid form until it is consumed (Misra et al., 1999). Enhances tablet disintegration, dissolution, drug absorption and onset of effect (Birudaraj et al., 2005).

Avoid gastric degradation of the drug in gastric and intestinal environment.

1.3 Approaches for fast disintegrating tablets

Conventional technologies for preparing fast dissolving tablets are as follows.

Lyophilisation (freeze drying) technique.

Tablet moulding technique

Spray drying method

Cotton candy method.

Mass extrusion technique.

Sublimation technique.

Direct compression technique.

1.3.1 Lyophilization (freeze drying) technique

Formation of amorphous porous product in freeze-drying procedure dissolves the drug rapidly and is exploited in preparation of fast dissolving tablets. Lyophilization is a technique that involves removal of the solvent from the drug in frozen solution or in suspension using structure-forming additives (Renon et al., 2000). In this process drug solution along with

polymer was poured in the preformed blister packs. These trays are then passed through tunnel of liquid nitrogen which freezes the drug solution or suspension. These blister packs are then charged into the refrigerator to continue for freeze drying. This method established improved absorption and increased bioavailability (Jaccard et al., 1985) and also gives glossy structure resulting in light weight and highly porous product (Azza et al., 2011). The major disadvantage is that this technique is very expensive (Habib et al., 2000), time consuming and fragility which makes the formulation unsuitable for conventional packaging for those products which show poor stability under stress conditions (Corveleyn et al., 1997).

1.3.2 Tablet molding technique

Tablet molding procedure is of two types. The first method (solvent method) consists of moistening of the powder bed with hydro-alcoholic solvent followed by compression at low pressure to appearance a wetted mass in molded plates i.e., compression molding. From this mass the solvent is separated by air drying. The prepared tablets by this method possess porous formation that hastens dissolution. The second method (heat molding method) involves preparation of suspension by mixing the drug with agar and sugar (manitol or lactose) then pouring them in blister packs, solidifying the agar at room temperature and drying at 30^0C under vacuum. The presence of the binding agents increases the mechanical strength of the tablets (Masaki et al., 1995). In this taste masking of the tablets is an additional problem. These drug particles were formulated by spray congealing the lecithin molten mixture, polyethylene glycol and drug into lactose containing tablet triturate appearance. Similar to the freeze drying technique the tablets produced by this technique are easier to develop for industrial manufacturing.

1.3.3 Spray drying method

In this procedure gelatin is used as a matrix forming agent, mannitol as a diluent, crospovidone, croscarmellose sodium and sodium starch glycollate are used as superdisintegrants. The tablets made using this method disintegrated within 20s in aqueous media (Allen et al., 1997). Highly porous product was obtained using this method (Allen et al., 2003).

1.3.4 Cotton candy method

This process is also called as candy floss and uses a spinning technique to produce floss-like arrangement, which looks like a cotton candy. The preparation, involves the formation of matrix using polysaccharides or saccharides by repeated action of flash melting followed by spinning (Meyers et al., 1995). The matrix which is produced is partly recrystallized to comprise enhanced flow properties (Pebley et al., 1994). This candy matrix is then subjected to milling process and then blended with drugs, additives and then compressed. This process can hold large drug doses and improve mechanical force. However it requires high temperature processing.

1.3.5 Mass extrusion technique

This type of expertise involves softening the blend of active ingredient using polyethylene glycol and methanol solvent mixture followed by subsequent removal of mass using the extruder or by using the syringe to get the product of cylinder into equal segments by using blade that is heated to shape into tablets. This cylinder is also used for the coating of granules having objectionable taste and thereby masking of bitterness can be done (Bhaskaran et al., 2002).

1.3.6 Sublimation technique

The key in quick disintegration of FDTs is to produce a porous formation in the tablet matrix. To make such a porous matrix in the tablets, volatile ingredients are involved in the process of sublimation. The ingredients such as ammonium carbonate, ammonium bicarbonate, camphor, urea, benzoic acid and naphthalene which are highly volatile can be compressed with other additives (Sharma et al., 2010). The volatile ingredients may be removed from the tablets by sublimation technique leaving behind a highly porous medium. Cyclohexane or benzene can be used for pore forming agents. The tablets prepared by this technique disintegrate in 10 to 20 seconds (Koizumi et al., 1997).

1.3.7 Direct compression technique

This technique is very simple and is generally a cost effective process which can be used for the preparation of FDT because of the improved availability of superdisintegrants and sugar based excipients (Kumar et al., 2010).

1.3.8 Superdisintegrants

Most of the FDT technologies are based on direct compression, using superdisintegrants which chiefly affects the rate of disintegration as well as dissolution. The existence of other water-soluble excipients and effervescents enhances the process of disintegration further.

1.3.9 Sugar based ingredients

This is one of the methods for preparing FDT by direct compression. They make use of bulking agents like mannitol, maltose, sorbitol etc. which exhibit more solubility and sweetness which impart taste masking property providing a satisfying mouth feel (Parul et al., 2006).

Takao et al (2005) classify sugar-based additives into 2 types based on the foundation of dissolution rate and moulding. Type-1 saccharides (mannitol and lactose) which reveal less mould ability but more dissolution rate. Type-2 saccharides (maltilol and maltose) disclose which provide more mould ability and less dissolution rate. In this method disintegration and solubilisation of tablet are due to the presence of superdisintegrants, water soluble ingredients and effervescent. The disintegration time is satisfactory though the efficiency is powerfully affected by the size and hardness of the tablet.

Conventional equipment, commonly available additives and fewer steps are involved in this technique. Elevated doses can be incorporated and the tablet's final weight can simply exceed compared with other techniques. This method is widely used in developing FDTs because of the increased accessibility of recipients.

Addition of disintegrant in FDTs leads to fast breakdown of tablets and therefore, more dissolution. Sodium carboxymethyl starch (sodium starch glycollate), cross linked polyvinylpyrrolidone (crospovidone), modified cellulose (croscarmellose sodium), soy polysaccharides, gellan gum, xanthan gum, cross-linked alginic acid, calcium silicate and ion exchange resins are used as superdisintegran ts. FDTs can also be obtained by including effervescent disintegrants, which generates CO2. The main disadvantage of effervescent disintegrants was its hygroscopic nature. Hence the manufacturers require humidity control

conditions and needs to provide safety of the finished product. This reflects by and large the price of the finished product.

1.4 Patented technologies

1.4.1 Zydis technology

In this method the drug is made to dissolve (entrapped) in fast dissolving carrier (Seager et al., 1998). When these formulations are placed in the mouth, the structure (freeze dried) disintegrates immediately and water is required for swallowing (Chang et al., 2000). Gelatin, dextran (alginates) was included for the strength of the tablets. Saccharides such as mannital or sorbital were added for crystallinity, elegance and hardness. Water is added in manufacturing process to get porous tablet and various gums are used for the prevention of sedimentation of dispersed drug particles. Collapse protectant such as glycine is included to avoid reduction of tablet during freeze drying process.

1.4.2 Durasolv technology

CIMA labs contain the Durasolv patented technology. In this technology the tablets consist of drug, diluents and a flow promoter. The tablets were prepared by conventional tablet punching machine and those tablets can be packed in blisters and this technology is useful for products having low amount of active ingredient.

1.4.3 Orasolv technology

This technique is invented by CIMA labs. The taste of active ingredient is masked and compressed at low compression forces to have lower dissolution time. The produced tablets are friable and soft.

1.4.4 Flash dose technology

This technology is originated by Fuisz. Nurofen meltlet which is a mouth tablet of ibuprofen uses flash dose technology and is the first product found by Biovail Corporation. These tablets contains matrix form self binding clip called as floss and are prepared by flash heating process.

1.4.5 WOW tab technology

Yamanouchi Pharmaceutical Company patented this technology. In this procedure, high and low moldable saccharides are used to get a strong tablet having fast melting. The active ingredient is mixed with lactose, mannitol, glucose and granulated with maltose, oligo saccharides and then compressed to get tablet.

1.5 Taste masking

Many techniques exist for covering the drug's bitter taste which includes taste masking with flavouring agents, sweetening agents and amino acids. Masking of taste is done by various methods such as polymer coating, conventional granulation.

1.5.1 Taste masking using sweetening agents, flavouring agents and amino acids

This method is used for masking of taste in chewable tablets and fluid preparations (paediatric) and is not useful for extremely harsh and water soluble drugs. Artificial flavouring and sweetening agents are usually worn with other taste-masking methods. The cooling effect of the taste masking agents helps in reducing the objectionable bitter taste. Menthol decreases the bitterness. Aspartame is a well-known sweetener in reducing the bitterness. A minute concentration i.e., 0.8% is useful in reducing the harsh taste of acetaminophen. Mannitol, starch, and lactose provided taste-masking of caffeine (Matsubara et al., 1990).

Artificial sweeteners like hesperidin dihydrochalcone 4'-β-D glycoside and neohesperidine dihydrochalcone have the capacity to cover bitter and salt tastes with lingering sweetness in them.

1.5.2 Taste masking using lipophilic vehicles

Poly-alcohols and lipids raise the mouth viscosity due to which the taste buds are coated and are called potential taste masking agents.

1. Guaifenesin melts granulation carnauba wax and veegum (magnesium aluminium silicate)

2. Cimetidine granulation GMS (glyceryl monostearate)

Lecithin and lecithin-like substances have power over objectionable taste in pharmaceuticals. Veegum along with soy lecithin is used to cover the disagreeable talampicillin hydrochloride taste. The drug is either dissolved or dispersed into chloroform.

1.5.3 Taste masking using hydrophilic vehicles

In this method drug particles possess a barrier in the form of coating, thus the drug and taste buds' interaction minimizes. Chewable tablets upon coating provide exceptional taste masking. Micro emulsion technique is used for masking the taste of the powders, chewable tablets and liquid formulations.

1.5.3.1 Carbohydrates

Orally given drugs can be taste masked by covering with carbohydrates. The bitter tasting drugs like pinaverium bromide, does not have objectionable taste when formulated by coating with cellulose or shellac mixture with polymer.

Masking the bitter taste of ibuprofen has been effectively done by air-suspension method to get microcapsules, which consist of core of crystalline ibuprofen along with eudragit coated chewable taste-masked character (Shen et al., 1996).

1.5.4 Taste masking using inclusion complexation

The drug molecule enters the opening of a complexing agent and forms stable complex. This agent is capable enough for covering the objectionable feel of drug by diminishing the oral solubility on swallowing, thus reducing the awareness of bitterness in taste. This technique is appropriate for lower doses of drugs. The Vander Waals forces are occupied in inclusion complexes (Nanda et al., 2002). β- cyclodextrin is used as a complexing agent which is sweet in taste, non-toxic and cyclic oligosaccharide which is obtained from starch.

The bitterness of carbetapentane citrate (syrup) was condensed to 50% by making 1:1 complex (cyclodextrin). Pleasant ibuprofen solutions are formed at 1:10 to 1:15 ratio with ibuprofen and hydroxypropyl β-cyclodextrin. The complex covered the bitter factor but produced sore taste, which was covered by sweetening agents.

1.5.5 Taste masking using ion-exchange resins (IERs)

These are high Mol. Wt. polymers having both cationic and anionic functional groups. These resins are mainly used in formulations for stabilizing the sensitive components, delaying in release of drug, breaking up the tablets, and to cover the taste. Drug can be incorporated by exposing the resin to the drug repeatedly in a chromatographic column or increasing the contact of resin within drug solution.

There is an attachment of drugs to the resin substrate thus forming insoluble resonates by means of ionic bonding; there by separation of the drug-resin complex does not take place below the salivary pH environment. This properly masks disagreeable taste and odor of the drugs.

The release of drug from the resin is complex and dependent on the resin properties and the ionic surroundings within the GIT. The drug molecules that are in attachment with the resin are exchanged with ions that have charge are present in the GIT and diffused out of the resins.

1.5.6 Taste masking using miscellaneous approaches 1.1.5.6.1 Effervescentagent

Effervescent agents were useful and are beneficial for oral management of drugs. They are used for masking the taste for dosage forms that have no intention to dissolve in water earlier to administration. A composition of chewing gum with objectionable taste medicament was formulated in such a way that it provides the medicament to the oral track. It consists of a base of

gum, an orally takable active ingredient, a taste masking agent (CO2), a composition of optional desensitization (anaesthetics like benzocaine, etc.) and other inactive materials, such as organoleptic additives and bulking agents. Recently, fentanyl and prochlorperazine effervescent tablets were formulated to supply these drugs for absorption to the oral tract.

1.5.6.1 Salt preparation

Salt preparation is one of the classical approaches to cover the bitter drug taste by either decreasing solubility or by increasing hydrophobicity by reducing contact of bitter drugs with the taste buds. This approach differs from others to alter the chemical composition of the drug substance to make it less soluble in saliva and therefore less stimulating the taste buds. Addition of alkaline metal bicarbonate like NaHCO3 covers the disagreeable taste of ibuprofen in watery medium. Objectionable taste of caffeine can be covered by forming as carbonated oral solid dispersion. Aspirin tablets are made bland by preparing aspirin in magnesium salts form.

1.5.6.2 Solid dispersion technique

In this technique, one (or) more drugs are spread in an immobile solid carrier. Solid dispersion of drug with the aid of polymers, sugar, or other appropriate agents is very practical for taste masking. The dimenhydrinate masking of bitterness can be done by formulating the solid dispersion of drug with polyvinyl acetate phthalate.

1.5.6.3 Group modification and pro-drug approach

The clarithromycin 2’ position’s alkyloxyalkyl carbonates have covered bitterness and enhanced bioavailability when given orally. Bland pro-drug of opioid drugs can be formulated for better buccal release. Bitter prodrugs of nalbuphine hydrochloride, naltrexone, naloxone,

oxymorphone hydrochloride, butorphanonol, and levallorphan can be manufactured for buccal route of administration to get better bioavailability comparative to oral dosing devoid of objectionable taste.

1.5.6.4 Freeze drying method

This technology is used in developing fast-dissolving ODTS like Zydis and Lyoc technology. As the freeze drying process produced high porosity, Zydis in its tablet shaped dosage form disassociates in the mouth within seconds.

In Zydis process the drug has to be dissolved in a water soluble structure forming agent. The mixture is then placed into the blister pockets and then freeze dried. Gelatin and manifold are most commonly used structural ingredients, starches and gums are the other suitable excipients. This process is preferred in low solubility drugs which are easily freeze dried.

1.5.6.5 Wet spherical and continuous melt method

To cover the bitter taste of enoxacin, this method of micro encapsulation process combined with this method was used.

1.6 Mechanism of tablet disintegration and water absorption

When mouth dissolving tablets are placed in the mouth, upon contact with saliva the tablets disintegrate or dissolve instantaneously. There are four mechanisms involved in the tablet disintegration mechanisms

Swelling

Wicking

Deformation

Disintegrating particle/particle repulsive forces

1.6.1 Swelling

The most commonly established mechanism of tablet breakup is swelling. The tablets with elevated porosity confirm poor disintegration because of lack of sufficient swelling force and on the other hand in tablets with low porosity, the swelling force is sufficiently exerted. The fluid cannot be penetrated into the tablet when the packing fraction is more, there by disintegration rate slows down.

1.6.2 Wicking

Capillary action mechanism is the first step in wicking. When the tablet is placed in the medium, it penetrates into the tablet and the air is replaced on particles, weakening intermolecular bond and tablet breaks into finer particles. The water taken by the tablet depends up on the hydrophilicity of the drug or ingredient and on surroundings of tabletting. For this type of disintegrants, porous structure maintenance, less interfacial tension in the direction of aqueous fluids are compulsory which creates a hydrophilic network around drug particles and helps in disintegration.

1.6.3 Deformation

During compression of tablet, the disintegrated particles deform and these particles obtain normal structure when they are contacted with aqueous media. When granules are deformed expansively during compression, the swelling ability of starch is enhanced. The deformed particles increase in size and produce a breaking of the tablet. The starch may be followed by this deformation mechanism and has to be studied.

1.6.4 Disintegrating particle/particle repulsive forces.

Guyot-Hermann has projected repulsion theory of a particle that non-swelling particles also cause disintegration of tablets. The mechanism of disintegration is due to electric repulsive forces between particles and in order to have that repulsive forces water is required (Lachman et al., 1990). This mechanism of repulsion is secondary to wicking.

2.0 AIM AND OBJECTIVES

In the present study the main objectives were

To develop fast disintegrating sublingual tablet formulations using zolmitriptan and rizatriptan (5-HTIB/ID receptor agonist) anti-migraine drugs.

To evaluate the powder formulations for Micromeritic properties.

To determine prepared tablets for physical parameters, *in vitro* release studies and characterization of optimized formulation.

To establish the stability of optimized formulation.

To compare *in vivo* release studies using rabbit as the animal model.

RESEARCH WORK PLAN

Literature review

Selection of excipients

Selection of superdisintegrants

Preparation of fast disintegrating sublingual tablets

Evaluation of sublingual tablets

Micromeritic properties of prepared powder formulations

Determination of physical properties of tablets

In vitro release studies

Characterization

Stability studies

Documentation of the results

Summary

Conclusion

3.0 LITERATURE REVIEW

Azza et al., (2011) developed fast disintegrating sublingual zolmitriptan tablets using freeze drying technique. They used gelatin as binder and manitol as matrix enhancing agent. The tablets disintegration and dissolution is enhanced with speeding the onset and drug absorption. This sublingual formulation gave faster and higher zolmitriptan plasma concentration in rabbits compared with oral marketed zolmitriptan formulation and constitutes an advance in migraine treatment.

Alessandro et al., (2010) have written a review on migraine. They described strong epidemiologic evidence linking migraine and stroke in adults. In their review four major issues are summarized. 1. Migraine ischemic stroke relation 2. Migraine with increased cardiovascular risk factors 3. Migraine specific drugs 4. Migraine and ischemic vascular events.

Debjet et al., (2009) wrote an overview on fast dissolving tablets. In that review they explained the tablets fast disintegration and dissolution in saliva without water within few seconds. They also explained the need of FDTs, their benefits, limitations, techniques for preparation of tablets, patented technologies, commercially available formulations, mechanisms of superdisintegrants, pre-formulation studies and the evaluation of those prepared tablets. They concluded that the problems experienced by the patients with conventional tablets can be overcomed by fast dissolving tablets.

Mohanachandran et al., (2011) made an overview on superdisintegrants. They described about the use of right disintegrates in order to have optimal bioavailability and to improve the efficacy of solid dosage forms. Generally superdisintegrants were used at low concentrations typically 1-10 % compared with the total formulation weight. In their review they

listed the various superdisintegrants being used in formulations which provide effective and safer delivery to the patient.

Shailesh Sharma et al., (2007) wrote a review on fast dissolving tablet: the future of compaction. They explained about the convenience of the fast dissolving formulations.

Avani et al., (2006) explained difficulties of swallowing conventional tablets and demands for orally disintegrating tablets particularly in children and in old age patients.

Sheeba et al., (2009) studied the effect of rising nifedipine load on fast disintegrating sublingual characteristics in emergency treatment of hypertension. This drug undergoes presystemic metabolism in the liver and gut wall. The bioavailability was found to be between 43%-77%. They prepared sublingual tablet as it bypasses the metabolism of the drug in liver so that the patient gets immediate relief from hypertension. In the preparation of sublingual tablet used various superdisintegrants. The Tablet was formulated using the direct compression technique. The evaluation tests of the prepared tablet was found to be satisfactory. The tablet have mixture of croscarmellose sodium and sodium starch glycolate, each 2mg showing fast dissolution and disintegration.

Mutasem et al., (2006) determined the epinephrine drug concentration from fast disintegrating tablets. The plasma concentrations are same as dose obtained after 0.3mg IM injection. They compared 0, 10, 20 and 40mg of epinephrine in sublingual tablets compared with 0.3mg intramuscular epinephrine injection, they used rabbit model for the study. They concluded that the tablet containing 40mg of drug in sublingual formation shows same results as that of 0.3mg intramuscular injection. So this shows that sublingual administration is one of the feasible alternatives to intramuscular injection.

Elina et al., (2011) investigated improvement of absorption of less water soluble, first-pass metabolised perphenazine with sublingual formulation. In order to increase the absorption they have included cyclodextrin and made solid dispersion which increases the solubility of sublingual formulation. They proved that sublingual absorption is further enhanced by micronization of perphenazine.

Toshihiro et al., (2003) developed lansoprazole fast disintegrating tablets which consist of enteric coated micro granules and inactive granules. They used manitol as the main excipient, HPC, microcrystalline cellulose and cross povidone as binders and disintegrants. They concluded that the tablet containing 47.4% of enteric coated micro granules gave sufficient strength and rapid disintegration in the mouth (<30s) and also did not show much effect in the acid or buffer stages of dissolution.

Emma et al., (1998) conducted pharmacokinetic studies on 2.5mg and 5mg oral doses of zolmitripton in women and men. They compared pharmacokinetics in women and men. The absolute bioavailability was found to be 0.41 and 0.09 after 2.5mg and it was found to be 0.48 and 0.36 after 5mg in women and men respectively. The AUC after 2.5mg dose was found to be 18.4hng/ml and 23.1hng/ml correspondingly, in men and in women. The AUC after 5 mg dose was found to be 32.7hng/ml and 60.2hng/ml respectively. They concluded that these differences do not have clinical significance. The AUC and C-max depends on dose and as a mean it was fallen 13% and 16% respectively when the drug is administered after taking food. They concluded that the oral bioavailability was good at therapeutic doses in healthy humans and also proved that dose dependent pharmacokinetics does not affect the presence of food to clinical extent.

Acharjya et al., (2010) developed three simple, accurate, precise and inexpensive UV methods. The drug exhibited maximum absorption at 0.5-20 µg/ml concentration at 227 nm and at the concentration of 0.5 to 8.0 µg/ml at 281 nm respectively.

They derivatized spectrum into 1st and 2nd order. The trough at 233 nm for D1 and crest at 238 nm for D2 were measured. From these two methods the drug showed linearity from 0.5-20 µg/ml. They concluded that this method shows good results in the concerning concentration range, accuracy, precision, robustness and ruggedness.

Sameer et al., (2009) studied presence of calcium silicate and lubricants on β-cyclodextrin based FDTs. They also evaluated the effects of moisture at 75, 85 and 95% RHs. They used factorial design to optimise the concentrations of calcium silicate as disintegration enhancing agent and magnesium stearate as lubricant. In the results they have concluded that the concentration of calcium silicate does not have any effect but though the presence of lubricant was very significant for degeneration and rigidity of the tablet. They found 1.5 percent of magnesium stearate gave 23.4seconds DT and hardness as 1.2kg. They also concluded that at 75% moisture the hardness does not have any effect where as at 85% and 95% treatment with moisture, the hardness of the tablet was increased. However the disintegration time was not effected.

Anupama et al., (2009) developed mouth dissolving tablets of oxcarbazepine to get desired and intended benefits. They used direct compression technology and solid dispersion method. In the first method they have used crospovidone and aspartame. In solid dispersion they used polyvinyl pyrrolidone K-30; PEG 6000 in various weight ratios. They concluded that solid dispersion technology was the better substitute to the direct compression technology for the

development of mouth dissolving tablets especially for the drugs that are less soluble in water.

Arjun et al., (2010) prepared rosiglitazone mouth dissolving tablets in diabetes mellitus for long therapy. Sodium starch glycollate, crospovidone and croscarmellose sodium were used as super disintegrants. The mouth dissolving tablets having 1:1 ratio of cros carmellose sodium and crospovidone showing maximum release of the drug. They also conducted stability studies at 40°C/75% relative humidity. The formulations were stable.

Honey et al., (2008) optimised and formulated fast disintegrating tablets of ondansetron HCI or domperidone using aminoacetic acid, carmellose and sodium alginate to prevent nausea and vomiting. They revealed that domperidone optimised FDTs better than domperidone FDTs containing cross carmellose or crospovidone. They concluded that this novel mixture of excipients can be used for deliverance of water insoluble drugs instead of superdisintegrants. Shapero et al., (2006) studied clinically an international open- label study. It includes new, substantial variables applicable to PCPs and recruits patient's present prime care who diagnosed migraine. They treated migraine attack/month with zolmitriptan ODT 2.5mg. 595 patients are treated with 7171 migraine attacks with ODT tablet. Out of those 504 of them finished six months questionnaire, 380 patients still wish to continue ODT tablet. From this study they indicated that patient-oriented end-points are significant and encouragable to the physicians than conventional end point, making them to decide on their own managing the migraine.

Rahul et al., (2009) studied and optimised fast disintegrating tablets in three stages and in each stage hardness, friability and disintegration time was studied and they revealed that in stage-I hardness and disintegration time improved with increased gelatine concentration. In stage-II saccharides like sorbitol, mannitol and sucrose in different ratios were added (10 percent

and 80 percent), good results were obtained with mannitol containing formulations which was carried for the next stage and in that stage (stage III) they have added polymers to enhance mouth feel and pre-gastric withholding (carbopol 974P-NF). Pluronic F127 (6%) showed increased disintegration time and viscosity without any change in mechanical properties.

Takao et al., (2005) studied on the improvement of compressibility of low compressible saccharides; modification of the particle was done by coating and granulating the low compressible saccharide with a high one. They also discovered that high compressible saccharides can also be used as a binder solution in the amorphous state after the completion of granulation stage. They concluded that the prepared tablets have sufficient hardness, fast disintegration time, manufactured by simple commonly available equipment and used for wide range of drug dosages.

Mutasem et al., (2006) have developed sublingual tablets of fast disintegrating epinephrine tablets. They have prepared four formulations with 0 percent, 6 percent, 12 percent and 24 percent of epinephrine bitartrate. The excipients used were MCC (PH-301), low-substituted HPC (LH11) and magnesium stearate and tablets were obtained by direct compression method. These tablets had been evaluated for physical parameters. In all the formulations hardness, disintegration time and wetting time was found to be suitable for sublingual administration.

Takuma et al., (2008) made an effort to produce fast disintegrating furosemide tablet using direct compression method. They used MCC, cros carmellose sodium, xylitol and sucrose stearic acid ester. The tablets produced using sodium starch glycollate by solvent (organic) evaporation technique and showed hardness >30 N and disintegration time was < 20s which was

concluded by them to be suitable for preparing fast disintegrating tablets.

Yara et al., (2009) evaluated bioequivalence of two commercial ondansetron 8mg tablets. They have used simple, sensitive, rapid, LC-MS method of ondansetron for determination in human samples. Bioequivalence between both was determined by 90% confidence interval for the Cmax ratios of AUC for the test and the reference products. They concluded that the test as well as reference formulations are bioequivalent.

Kilic et al., (2007) developed a specific and sensitive LC-MS method for zolmitriptan and their metabolites determination in human samples. The internal standard and analytes (paroxetine) were extracted with ethyl acetate: dichloromethane (4:1) and were separated using isocratic mobile phase in XTerra RP18 column. This validated method was used in pharmacokinetic studies. The mobile phase consists of acetonitrile, 5mM ammonium acetate and formic acid (50:50:0.053, vole/vole/vole).

Vijayakumar et al., (2010) developed a sensitive, specific, linear, stability indicating Hp-LC method for the analysis of zolmitriptan related substances. They concluded that this method is used for detecting, quantifying impurities (known and unknown) and degradation products during routine analysis of zolmitriptan and stability studies.

Asad et al., (2007) developed simple, rapid, gainful and extraction gratis Spectrophotometric method for zolmitriptan determination in formulations. In this method they made a reaction of zolmitriptan in acetonitrile with 0.2% 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone to form a colour product and showed absorbance at 555 nm. They concluded that this method can be used for determination of zolmitriptan in formulations.

Sharma et al., (2010) prepared MDTs of domperidone using camphor and crospovidone with the help of direct compression method. By exposure to vacuum the camphor was sublimed. These tablets were subjected for friability and disintegration time. They found that the tablets with optimum concentrations of camphor and higher percentage of crospovidone results in rapid disintegration.

Kumar et al., (2010) developed mouth dissolving tablets of sildenafil citrate using CCS, CRP, MCC and starch by direct compression method. They concluded that tablet containing crospovidone and croscarmellose sodium between 2-8% was disintegrated quickly (30s).

Prashant et al., (2010) developed and evaluated mouth dissolving meloxicam tablets. The tablets were manufactured by wet granulation. The ingredients used were crospovidone, colloidal silica dioxide, camphor, lactose and PVP solution in ethyl alcohol. The prepared tablets were subjected for physical tests. They found that the formulation containing camphor and rospovidone effects the parameters like wetting time, disintegration time and percentage friability and also concluded an effective vacuum drying technique which is an important alternative approach in place of more expensive adjuvant.

Takao et al., (2008) developed taste masked fast disintegrating famotidine tablets using spray dry method. The excipients used were aqua coat ECD30 and Eudragit NE30D or triacetin. They established that the spray dried process produced flavour masked particles for FDTs.

NEED FOR INVESTIGATION

The require for patient compliance dosage forms were increased since last decade. This has lead to the development of new techniques. The development of new drug formulations is time consuming and expensive these days. So increased efforts is a challenge for researchers in producing cost effective dosage forms for the development of new dosage forms using existing drugs. Currently tablets and capsule dosage forms are available as drug delivery systems. However, patient groups like geriatric, paediatric, mentally retarded and uncooperative will not prefer to take conventional dosage forms (Prajapati et al., 2009). To fulfil these needs the researchers have invented novel oral dosage forms known as fast disintegrating tablets that disintegrate quickly in the saliva within few seconds without using water. Sublingual route of administration produces quicker commencement of action than conventional tablets and part absorption from the blood vessels of sublingual route bypasses the first pass effect (Birduraj et al., 2005).

Various methods are used to devise fast disintegrating tablets (Allen et al., 2003).One of the easiest and cost effective tablet techniques which require incorporation of superdisintegrants and highly water soluble excipients to get fast disintegration and dissolution. Water or heat is not required in this technique during preparation and it is most ideal for drugs which are moisture and heat sensitive.

Migraine affects 6% in males and 18% in females with 34 attacks per year for men and 37 attacks per year for women (Lipton et al., 1993; Hu et al., 1999). It is characterised by unilateral, pulsating moderate to severe headache (Fenuik et al., 1985; Stovner et al., 2006), commonly accompanied by nausea, vomiting, phonophobia and photophobia (Zimma et al.,

2011). The attack lasts for 4-72 hrs in adults (Launer et al., 1999). Two types of migraine are identified i.e., migraine with aura and migraine without aura. Major issues considered in migraine are cervical artery dysfunction (Hedlund et al., 2009), increased prevalence of cardiovascular risk factor caused due to migraine specific drugs (Lipton et al., 2004), analgesic over doses, refractory migraine, migraine in elderly, during pregnancy and menstrually triggered migraine. It is believed to be due to the release of serotonin chemical or 5HT to the blood stream from its storage site resulting in changes in neurotransmitter and blood vessels in the brain. This causes pain in neurons and the blood vessels wall become irritated.

Zolmitriptan is class-III drug, serotonin 5-HT receptor agonists and widely used in the treatment of migraine. The symptoms of migraine include pain, nausea and photophobia or phonophobia (Marcelo et al., 2003). This drug is completely absorbed followed by oral administrations. The therapeutic activity of the drug is due to agonist effect at the 5-HT IB/ID receptors on intra cranial blood vessels, trigeminal system sensory nerves which causes constriction of cranial vessel and the inhibition of release of pro-inflammatory neuropeptide. Some triptans are available by means of various routes of administration apart from oral tablets like ODTs, rectal suppositories and intranasal administration, etc. Current methods of administering anti-migraine drugs suffer from major efficacy limitation due to degradation in the GIT and low absorption of the drug. Oral formulations of anti-migraine drug has large doses (20-30mg) leading to nausea, vomiting and other adverse effects. Most of the anti-migraine drug is subjected to first pass metabolism. Low bioavailability and slow onset causes the drug to be completely absorbed following oral administration of action and large inter-subject variability.

Injectable forms need lower dose as related to other non-injectable methods of administration which causes inconvenience of an injection and problems with the self administration are self evident.

3.1 Advantages of sublingual route.

Enhances tablet disintegration and dissolution

Speeding drug absorption and onset of effect

Avoid first pass hepatic metabolism

Avoid gastric irritation, nausea and vomiting

Reduction in the dose there by minimizing the frequency of dosing

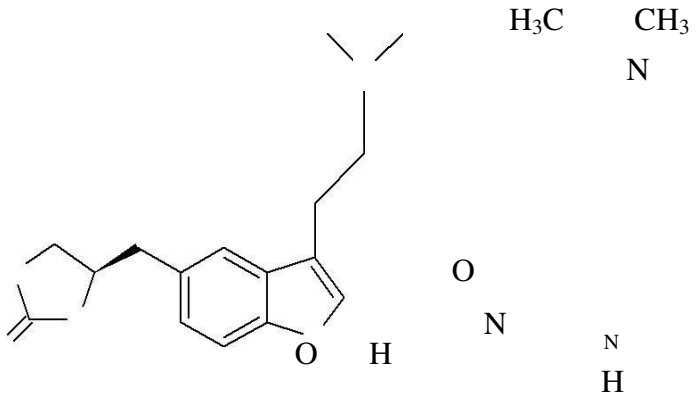
Convenient for administering to children and elderly people

3.1 DRUG PROFILE

Zolmitriptan

Zolmitriptan belongs to selective 5-hydroxytryptamine 1B/1D receptor agonist.

Structure:



IUPAC name: (S)-4-[[3-[2-(dimethylamino) ethyl]-1H-indol-5-yl] methyl] xazolidinone.

CAS NO: 139264-17-8.

Mol. For.: C16H21N3O2.

Mol. Wt.: 287.36 gm/mol.

Phy. State: White or almost white powder. M.P: 136 to 141°C.

Category: Anti-migraine

Solubility: Slightly soluble in water and freely soluble in 0.1M HCL. Dose: 2.5mg, 5mg up to10mg (maximum).

Half life: 2 to 3 hours.

Bioavailability: Approximately 40% absolute bioavailability. Absorption: Well absorbed through GIT.

3.2.1 Metabolism: It is converted into N-desmethyl metabolite which is active such that the concentration of metabolite is about 2/3rd of zolmitriptan as the strength of metabolite is 2-6 times that of parent and contributes a major part on the whole effect after zolmitriptan administration (Dowson et al., 2005).

3.2.2 Adverse effect: Tightness in the chest, bluish tongue to the skin, cold arms and legs, dizziness, drowsiness, rashes on skin, swelling of the eye lids or face, smallness of breath.

Stability: Stored at room temperature, protected from heat, moisture and sunlight.

3.2 POLYMER PROFILE

3.2.1. Sodium starc h glycollate

Pregelatinized starc h occurs as moderately coarse to fi nd powder, white to off-white in colour, odourless with slight characteristic taste.

Mol. for: (C6H10O5)n. Non-proprietary

names: BP: Pregelatinized starch

PhEur: Amylum preg elificatum

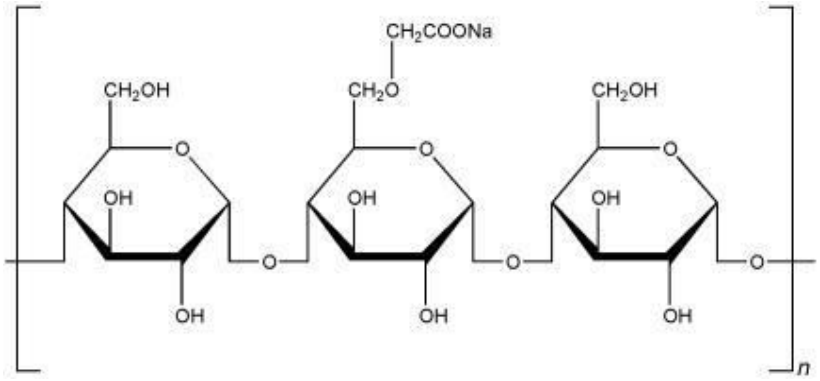
USPNF: Pregelatinize d starch.

Synonym: Compress ible starch, lycatab C, Instastarch, lycatab PGS, merigel.

CAS No.: 9005-25-8

Che. name: Sodium carboxymethyl starch

Structure:



Category: Tablet and capsule diluent, disintegrant and binder.

Applications in pharmaceutical technology: Widely used as binding agent, diluents and disintegrating agent in tablet an d capsule formulations (Jarosz et al., 1982), it is used as a binder in tablets

(Suzuki et al., 1976). In those formulations, this pregelatinized starch is self lubricating. When it is used with other excipients there is a need of adding lubricant (Pilpel et al., 1971). Pregelatinized starch can also be used in wet granulation process.

Tablets prepared with this have good storage properties (Gordon et al., 1990) and are stable. It is stored in properly closed container and protected from moisture and temperature. The physical nature of sodium starch glycol late remains unchanged for 3-5 years at moderate temperatures and humidity.

Incompatibilities: Incompatible with ascorbic acid (Botha et al., 1987). Safety: SSG is extensively used in oral formulations and is considered as non-hazardous and non-irritant material.

3.3.2 Croscarmellose sodium

Croscarmellose sodium is a cross linked sodium carboxymethyl cellulose polymer.

Nonproprietary names:

Croscarmellose sodium- BP

Carmellosum natricum conexum- PhEur

Croscarmellose sodium- USPNF \

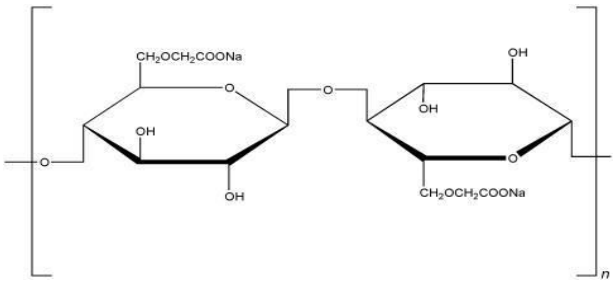
Synonym: **Ac-Di-Sol;** cross linked carboxymethylcellulose sodium; Explocel; cellulose gum modified; Nymcel ZSX; Pharmacel XL; Primellose;

Che. name: Cellulose, carboxymethyl ether, sodium salt, cross linked

CAS No.: 74811-65-7

Molecular weight: 9 0,000 to 70,000

Structure:



Category: Tablet and capsule disintegrant.

Applications:

It is used as disintegrates in granules, tablets and capsules (Dahl et al., 1991; Ferrero et al., 1997). In tablet formulations, it may be used in dry and wet methods. In wet granulation process, the croscarmellose sodi um can be included in both stages, so that the wicking, swelling ability of the croscarmellose sodium is utilized (Gordon et al., 1993). Up to 5% w/w concentrations can be used as disintegrant, but no rmally 2% w/w was used in the tablet s which are prepared by direct processes of manufacturing and concen tration 3% w/w can be used for wet-granulation method.

Physical Description:

White or greyish-white odourless powder.

Storage conditions:

Though it is a hygroscopic material but is stable. It must b e stored in a cool, dry place in a well closed container.

Safety:

Mainly used as a disintegrant in oral formulations and is nontoxic and non-irritant material.

3.2.3 Crospovidone

Synthetic photopolymer of N-vinyl-2-pyrrolidinone.

Nonproprietary name:

BP: Crospovidone

PhEur: Crospovidonum

USPNF: Crospovidone Synonym:

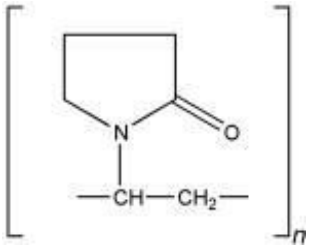
Cross linked povidone; E1202; Kollidon CL-MPolyplasdone XL- 10; Kollidon CL; **polyvinylpolypyrrolidone;** PVPP; Polyplasdone XL; 1-vinyl-2-pyrrolidinone homopolymer.

Che. Name: 1-Ethenyl-2-pyrrolidinone homopolymer CAS No.: 9003-39-8

Mol. Formula: (C6H9NO)n

Mol. weight: 1 000 000

Structure:



Category: Tablet disintegrant.

Applications:

As tablet disintegrant, dissolution agent (2–5%) in ta blets which are prepared by direct, wet and dry processes (Hipasawa et al., 2004). It quickly shows high capillary action and pronounces hydration capacity, with sma ll tendency in gel formation. The big particles exhibit a quicker disintegration than smaller once. It can also be used for enhancing solubility.

Physical description:

White or Off-white free-flowing tasteless, odourless hygroscopic material.

Storage conditions:

Hygroscopic, stor ed in closed airtight container in a dr y and cool place.

Incompatibilities:

Compatible with mo st organic and inorganic excipients, when it is contacted with water, crospovidone form molecular adducts with other materials.

Safety:

Used in oral products and is considered as a nontoxic, non- irritant.

3.2.4 Microcrystalline cellulose (Avicel pH102)

Purified partially polymerized cellulose

Nonproprietary name:

Microcrystalline cellulose- BP

Microcrystalline cellulose- JP

Cellulosum microcristallinum- PhEur

Microcrystalline cellulose- USPNF Synonym:

Avicel PH; cellulose gel; Celphere; Celex; Ceolus KG; E460; Emcocel; Ethispheres; Fibrocel*;*

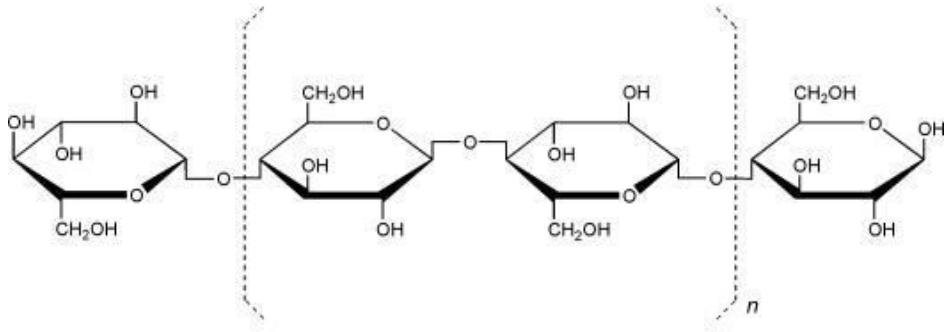
Pharmacel; crystalline cellulose; Tabulose; Vivapur.

Che. Name: Cellulose CAS NUMBER: 9004 34-6

Mol. For: $(C_6H_{10}O_5)_n$ where n=200.

Mol. Weight: 36,000.

Structure:



Category:

Adsorbent; suspending agent; diluent for tablets, capsules and as a disintegrate for table.

Applications:

Widely used as binder, diluent in formulations of tablet and capsule. In tablets it is used in both compression techniques (Wallace et al., 1983). In addition to this it also used as lubricant and disintegrant (Omray et al., 1986) in tablet manufacturing. Microcrystalline cell ulose is also used in cosmetic formulations and in food products.

Physical description:

White, odorless, tasteless, crystalline powder having porous particles.

Storage conditions:

Though it is hygroscopic material but it is stable. This should be stored in a cool and dry place preferably in air tight container.

Safety:

It is commonly used in oral, food products and is co nsidered as nontoxic and non-irritant. Consumption of huge quantitie s may havelaxative effect, although it is not having problem when included in pharmaceutical formulations as an excipient (Cooper et al., 1983).

3.2.4 Mannitol (D-mannitol)

It is a hexahydric alcohol associated with mannose and is isomeric with sorbitol.

Mol. formula: C6H14O6.

Mol. weight: 182.17

Category: Sweetening agent, diluents for tablets and capsule, tonicity agent, vehicle for lyophilized formulations.

Description:

White, odorless, crystalline or free flowing granules. It is having sweet taste and the sweetening powder is similar to glucose and half sweet as sucrose and also gives cooling sensation in the mouth. Mannitol shows polymorphism phenomenon.

Application:

In pharmaceutical preparation it is chiefly used as a tablet diluting agent (10-90%).

3.2.5 Aspartame

Nonproprietary names:

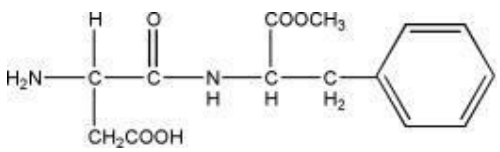
BP **:** Aspartame

PhEur **:** Aspartamum

USPNF **:**Aspartame

Che. Name **:** N-α-l-Aspartyl-l-phenylalanine 1-methyl ester

Structure:



Category: Sweetening agent.

Applications:

It is intensely used as a sweetening agent in beverage products, food products, in pharmaceutical preparations includ ing tablet formulations (Joac him et al., 1987), powders and in vitamin preparations. It improves flavour and it can be used to co ver some of the disagreeable t aste characteristics. This has 180-200 times sweetening power compared to sucrose.

Storage conditions:

It is stable in dry conditions. Hydrolysis occurs due to the presence of moisture and forms l-Aspartyl-l-phenylalanine , 3-benzyl-6-carboxymethyl-2, 5-diketopiperazine and β-l-Aspartyl-l-phenylalanine methy l ester.

Safety:

Aspartame is most widely used in oral pharmaceutical dosage formulations, in bev erages, and in food preparations as a powerful sweetener and is considered as nontoxic material. The W HO has set suitable daily dose ingestion for aspartame at 40 mg/kg b ody-weight (FAO/WHO 1981).

3.2.6 Magnesium stearate

It consists of mixture of solid organic acids containing variable portions of stearate and palmate of magnesium.

Nonproprietary name:

Magnesium stearate- BP

Magnesium stearate-JP

Magnesii stearas-PhEur

Synonym:

Magnesium octadecanoate, magnesium salt, octadecanoic acid, stearic acid and magnesium salt.

Chemical name: Octadecanoic acid magnesium salt. CAS No.: 557-04-0

Stru. Formula: [CH3 (CH2)16COO] 2 Mg. Mol. Weight: 591.34

Category: Lubricant for tablet, capsule.

Applications:

Magnesium separate was commonly used in cosmetics, pharmaceuticals and in food industry. It is chiefly used as flow promoting agent in capsule, tablet manufacturing at 0.25% w/w and 5.0% w/w concentrations. It is also found as an excipient in barrier cream.

Storage conditions:

Stable and stored in an air tight container preferably in cool, dry place.

Safety:

Used as pharmaceutical ingredient and is considered as nontoxic for oral formulations.

4.0 METHODOLOGY

CCS	:	Croscarmellose Sodium
SSG	:	Sodium Starch Glycollate
CP	:	Crospovidone
GIT	:	Gastro Intestinal Tract
hr	:	Hour
mg	:	Milligram
mm	:	Milli meter
nm	:	Nano meter
min	:	Minute
mI	:	Millitre
cm	:	Centimeter
N	:	Normality
mA	:	Milli ampere
kv	:	Kilo volts
RPM	:	Revolution per minute
s	:	Second
USP	:	United State of Pharmacopoeia
UV	:	Ultraviolet
wt	:	weight
w/w	:	Weight by weight
w/v	:	Weight by volume
v/v	:	Volume by volume
mcg	:	Microgram

%	:	Percentage
Lit	:	Litre
Vol	:	Volume
°C	:	Degree Centigrade
FDT_S	:	Fast Disintegrating Tablets
FDA	:	Food and Drug Administration
F	:	Formulation
FTIR	:	Formulation
SEM	:	Scanning Electron Microscopy
SD	:	Standard Deviation
Qty	:	Quantity
µ	:	Micron
µm	:	Micro meter
µg	:	Micro gram
µg/ml	:	Microgram per milliliter
Kg/cm^2	:	Kilogram per centimeter Square
amu	:	Atomic mass unit
M/z	:	Mass to charge ratio
cm^{-1}	:	Reciprocal centimeter of wave number
µl	:	Micro litre
θ	:	Theta
∞	:	Infinity
α	:	Alpha
σ	:	Sigma

λ	:	Lamda
β	:	Beta
≤	:	Less – than or equal to
≥	:	Greater – than or equal tp
B.wt	:	Body Weight
COA	:	Certificate of Analysis
Conc	:	Concentration
G	:	Gram
ID	:	identification
V	:	Volt
µA	:	Micro Ampere
LC –MS/MS	:	Liquid Chromatography – Mass Spectroscopy / Mass Spectroscopy
BLQ	:	Below Limit of Quantification
ISTD	:	Internal Standard
QC	:	Quality Control
CC	:	Calibration Curve

5.0 FORMULATION OF ZOLMITRIPTAN SUBLINGUAL TABLETS

5.1 EXPERIMENTAL METHODS

5.1.1 Preparation of calibration curve of zolmitriptan in 0.1N hydrochloric acid

10mg of zolmitriptan was dissolved in 0.1N hydrochloric acid and volume was made up to 10ml in volumetric flask (1000 µg/ml). From this 1ml was diluted to 10ml to get the stock solution containing 100 µg/ml concentrations. 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 and 0.8ml of this solution was more diluted to 10ml with 0.1N hydrochloric acid to get 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 7 µg/ml and 8 µg/ml concentration of zolmitriptan. The absorbance had been measured at 223 nm on a UV-VIS spectrophotomer (Schimadzu UV-1601) against 0.1N HCl as blank. A graph of concentration versus absorbance was plotted (Figure-2.1).

5.1.2 Calibration curve of zolmitriptan in mixture of buffer (pH4.0) and acetonitrile (90:10)

5.1.2.1 Standard and sample zolmitriptan drug solutions preparation

Accurately weighed about 50mg of zolmitriptan standard and transferred into a 50ml standard flask, dissolved and made to the mark with the same mobile phase (mix buffer (pH4.0) and acetonitrile (90:10)). From this, take 5ml of the solution into 50ml standard flask and make up the volume. The sample solution was set by taking NLT 20 tablets containing each 5mg of zolmitriptan. Approximately 20 tablets were taken and powdered in a mortar. The powder quantity equivalent to 50mg of zolmitriptan was weighed and transferred to the 50ml volumetric flask, dissolved this in mobile phase and diluted up to the mark with the same. From this take 5ml of the above solution into the 50ml standard flask and the volume was made with the same mobile phase.

5.1.2.2 λ max determination of zolmitriptan

Standard dilution of 100 µg/ml solution was scanned between 200nm-400nm using UV-VIS spectrophotomer (Schimadzu UV-1601). Based on the maximum absorption of the drug, the λ max was found to be at 210nm.

5.1.2.3 Preparation of mobile phase

Mixture of buffer (pH4.0) and acetonitrile in the ratio 90:10

5.1.2.4 Preparation of Buffer

6.80gms of potassium dihydrogen orthophosphate (KH2PO4) was taken into a 2000 ml beaker containing 1000ml of Milli –Q water. The buffer dissolved and the pH of the solution was adjusted by using orthophosphoric acid. After adjusting the pH (4.0), the solution was filtered through 0.45µm membrane filter and degassed in the sonicator.

5.1.2.5 Calibration curve of zolmitriptan

Standard solutions of zolmitriptan were prepared in concentrations between 25µg/ml and 150µg/ml. 50mg of zolmitriptan was dissolved in mobile phase and volume was made to 50ml with the same mobile phase (1000µg/ml). From this 2.5ml, 5ml, 10ml, 12.5ml and 15ml of the stock solution was taken and further diluted to 100ml to get 25, 50, 100, 125 and 150µg/ml.

A 10µl of the drug solution was injected at a flow rate of 1.0ml/min into the column. The detection wavelength was monitored at 210nm wave length. The temperature of column was kept at 30°C. Each solution was injected for six times and corresponding chromatograms

was obtained. The graph was plotted between concentrations in µg/ml versus peak area (Figure-2.3).

5.2 PREPARATION OF SUBLINGUAL TABLETS USING DIRECT COMPRESSION TECHNIQUE

In present study direct compression technique was used for the preparation of fast disintegrating sublingual tablets of zolmitriptan using superdisintegrants like sodium starch glycollate, croscarmellose sodium and crospovidone (Shangraw et al., 1989; Andries et al., 2003). The excipients such as mannitol (100mg) and avicel pH102 (microcrystalline cellulose) (23% to 27%) were selected as diluents. Aspartame (0.5%) was used as sweetening agent and magnesium stearate (1.0%) was selected as lubricant in this study Gohel et al., 2005; Anupama et al., 2009)..

Based on preparations availability in market, tablet weight was fixed. The excipients details were collected from USFDA recommended guidelines. Based on the disintegration time, various concentrations of super disintegrating agents were used. Most widely used superdisintegrants like sodium starch glycollate, croscarmellose sodium and crospovidone were used and their concentrations were optimised to get better wetting and disintegration time of tablets (Debord et al., 1987).

Prepared sublingual tablets using method of direct compression. Accurately weighed 5mg of zolmitriptan. After passing through sieve number 60 (Standard test sieves) all excipients were homogenously mixed using geometric dilution. Finally magnesium Stearate (Rameshwari et al., 2009; Keny et al., 2010) was added for lubrication and triturated well. Total nine formulations were prepared. In all the formulations, the superdisintegrant

concentration was varied between 2-6%. In first three formulations sodium starch glycollate concentrations were as 2%, 4% and 6%, the second three formulations had croscarmellose sodium as 2%, 4% and 6% and the last three formulations had crospovidone as 2%, 4% and 6%. Different concentrations of excipients were used to prepare various formulations of sublingual tablets (Al-Ghananeem et al., 2007). The blended material was compressed on 8mm standard concave punch using a minipress (RIMEK, India) tablet punching machine.

The total weight of tablet was made up to 150 mg (table-2.1).

Table-1: Composition of zolmitriptan formulations.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F
Zolmitriptan	5	5	5	5	5	5	5	5
Sodium starch glycollate	3	6	9	-	-	-	-	-
Croscarmellose sodium	-	-	-	3	6	9	-	-
Crospovidone	-	-	-	-	-	-	3	6
Avicel 102	39.75	36.75	33.75	39.75	36.75	33.75	39.75	3
Aspartame	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0
Mannitol	100	100	100	100	100	100	100	1
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1
Total Weight (mg)	150	150	150	150	150	150	150	1

Each tablet contains 5mg of zolmitriptan.

6.0 EVALUATION OF ZOLMITRIPTAN SUBLINGUAL TABLETS

6.1 Evaluation of Blends

The flow properties of the powder were very important in handling and processing operations. Hence the following Micromeritic properties were studied on the zolmitriptan powder formulations.

6.1.1 Angle of repose (θ)

It is described as the maximum possible angle among the surface piles of powder to the horizontal plane (Lachmann et al., 1998).

$$\tan(\theta) = \frac{h}{r}$$

$$\theta = \tan^{-1}(h/r)$$

Where θ - repose angle h-is height in cm r –is radius in cm

The angle of repose was measured by means of conventional fixed funnel process. 100 gm of the drug powder had flown through the funnel which was fixed to the stand at a fixed height (h). Then the radius and height of the powder bed was measured.

6.1.2 Bulk density (Db)

This is defined as the ratio of mass of the powder to the volume of powder bulk. It was determined by placing 100 gm of powder material into the measuring cylinder and noted the initial volume of the powder. This is called as a bulk volume. Through this bulk volume, bulk density was calculated by using the following formula.

$$Db = \frac{M}{Vb}$$

Where M is powder mass.

Vb is powder bulk volume.

Db is bulk density.

6.1.3 Tapped density (Dt)

It is defined as the ratio of total powder mass to the tapped volume of powder. This was determined by tapping the 100 gm of powder for 750 times and noted the volume using tap density tester USP (Tap density Tester, Electro lab ETD-1020). The tapping is further continued till the differences between two successive volumes is <2% and is expressed in gm/ml, given by

$$Dt = \frac{M}{Vt}$$

Where M is powder mass. Vt is powder tapped volume.

Table-2 Powder flow properties and angle of repose

Flow Property	Angle of repose (degrees)	Compressibility Index (%)	Hausner's Ratio
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair-aid not needed	36-40	16-20	1.19-1.25
Passable-may hang up	41-45	21-25	1.26-1.34
Poor-must agitate, vibrate	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very, very poor	> 66	> 38	> 1.60

6.1.4 Carr's Index (Compressibility percentage)

It can be calculated from bulk and tapped density which shows powder flow properties and is expressed as

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where Dt -tapped density of the powder and Db - bulk density of the powder

Hausner's Ratio

It is an indirect index of easy of powder flow and is calculated from the bulk and tapped density of zolmitriptan sublingual powder formulation, it is expressed as (Aulton et al., 1988)

$$\text{Hausner's ratio} = \frac{Dt}{Db}$$

Where Dt is powder tapped density and Db is powder bulk density.

6.1.5 Determination of physical properties of tablets

The tablets from each formulation were subjected to the following tests (Kumar et al., 2010).

6.1.6 Appearance

The general appearance of the tablet, and overall elegance and visual identity is very much needed for consumer acceptance.

6.1.7 Tablet thickness and diameter

Thickness and diameter of tablet is very important characteristic in reproducing appearance. Some filling equipment utilizes the counting mechanism to get uniform thickness. Randomly 10 tablets were taken from each formulation and the thickness and diameter was determined with a vernier caliper (Mututoyo, Japan). The size of the tablet should be dimensionally described, monitored and controlled.

6.1.8 Weight variation

A group of 20 tablets were taken from each formulation randomly and weighed using an electronic balance (Mettler-Toledo, PB303-S/FACT, Switzerland) and the average weight of the tablets was determined. The individual tablet weights were compared with average weight.

Table-3 Uniformity of weight

Tablet average weight	Percentage difference allowed
≤80	±10
Between 80 and 250	±7.5
>250	±5

6.1.9 Hardness of tablets

Strength of the tablet is defined as tensile strength (N: Newton). The crushing load on tablet is defined as the force necessary to fracture a tablet into 2 halves by applying compression (Ketan et al., 2002). The hardness of the tablet was measured by tablet hardness tester (Tab machines, India).

6.1.10 Friability

It is a measurement of mechanical strength of tablet. The friability is determined to evaluate the effects of rubbing and shocks which may frequently cause tablet to damage, cap or rupture. For this purpose Friabilator (Electro lab, India) was used (Metallic et al., 2000). A pre-weighed group of 20 tablets was located in the fabrilator and subjected for 100 revolutions (USP/NF, 2003). The dusted tablets were then reweighed. Compressed tablets must not drop more than 1% of their weight.

The friability (F) is expressed by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

6.1.11 Wetting time

Wetting time related with contact angle which is significant parameter required for fast dissolving tablets. The tablets with lesser wetting time have faster disintegration. The tablet wetting time was performed using simple procedure and it was done by placing the tablet on tissue paper which was located in a Petri-dish of 6.5 cm in diametercontaining 10ml of water at room temperature. The complete wetting time of the tablet was recorded (Honey et al., 2008).

6.1.12 Disintegration time *in vitro*

The tablets disintegration time was one of the important factors which are supposed to be optimized in development of the sublingual tablets. This test is carried out as per US FDA recommended guidelines for disintegration of zolmitriptan orally disintegrating tablets. This was tested on six tablets using Disintegration tester USP (Electro lab, ED-2AL, India), in distilled water at 37°C ±2°C (USP/NF, 2003). The complete disintegration of tablets without leaving palpable mass on the surface of mesh screen of basket assembly was noted.

6.1.13 Water absorption ratio

6ml of water was located in a Petri-dish and above this water a small tissue paper bend twice was located. The previously weighed tablet was placed gently on it and time taken for total wetting was noted. The weight of wetted tablet was noted.

$$\text{Water absorption ratio (R)} = \frac{Wa - Wb}{Wb} \times 100$$

Here Wa and Wb are weight of tablet after and before absorption of water

6.1.14 Dissolution *in vitro*

For all the formulations the *In vitro* dissolution were studied (Andries et al., 2003); with the help of a USP dissolution test apparatus type II i.e., Paddle method (Lab India, DS 14000, India) at a rotating speed of 50 rpm according to US FDA guidelines (Toshihiro et al., 2003). Freshly prepared 0.1N hydrochloric acid of 500ml was placed in dissolution vessels of dissolution apparatus (USP, apparatus II paddle method).The tablets were placed in a dissolution media at 37±0.5^{0}C temperature and the paddles were rotated at a speed of 50

RPM. 10ml of sample were collected and filtered using a 0.45µm pore size PVDF filter. The sample volume was immediately replaced in vessels with same volume of fresh 0.1N hydrochloric acid. The samples were collected at fixed times like 5min, 10min, 15min, 20min, 30min, 45min and 60 min, diluted and analysed for drug substance with a UV-Visible spectrometer (Schimadzu, model UV1601, Japan) set at 223nm. The amount of the drug release from the tablets at definite intervals was calculated by using standard graph of zolmitriptan.

6.1.15 Uniformity of content

20 tablets were arbitrarily selected and weighed and the average weight was calculated. The tablets were then powdered in a glass mortar. Drug content uniformity (USP/NF, 2003) was measured by dissolving and diluting the crushed tablets powder in mobile phase (90:10 %(v/v)) mix buffer (pH 4.0) and acetonitrile) and filtered through 0.45 µm membrane filter which was degassed. It was made necessary dilutions and analysed by using High Performance Liquid Chromatography (HPLC-Agilent 1100 series, USA) at the wavelength of 210nm. The liquid chromatography equipped with UV detector and column YMC-pack ODS-AQ (150x4.6mm, 5µm) was used. Isocratic elution was down at a flow rate 1 ml per min. The volume of injection was 10µl and the temperature of the column was 30°C.

6.1.16 Characterisation of zolmitriptan sublingual tablets

6.1.17 Scanning Electron Microscopy (SEM) studies

The surface characteristics of the zolmitriptan sublingual tablets and standard zolmitriptan were studied using Scanning Electron Microscope (SEM) (Scanning Electron Microscopy, JEOL 5400, Japan). The samples were attached on a brass stub by using a twofold sided adhesive tape (Rahul et al., 2009) and it was made electrically conductive by coating it 5-6 times and formed a layer of gold on it. Then SEM images were measured at an acceleration voltage of 5 kv.

6.1.18 STABILITY STUDIES

Optimized formulations (F9) were tested for stability studies by placing the tablets in the stability chamber (Thermo lab, USA) at 40±2^{0}C/75±5% RH up to 3 months. The tablets were analyzed at a time interval of 30 days for drug content, hardness, friability, wetting time and *in vitro* disintegration time.

7.0 RESULTS AND DISCUSSION

7.1 Calibration curves of zolmitriptan

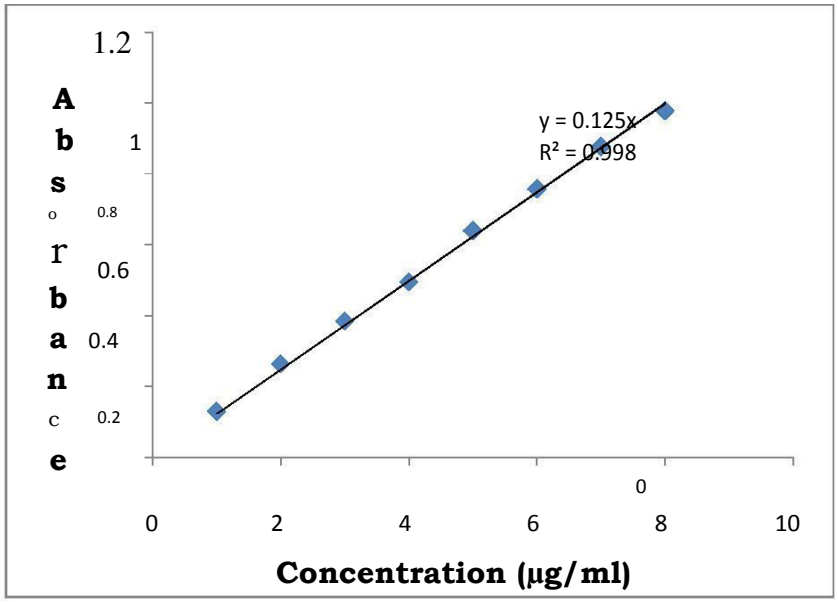
7.1.1 Calibration curve of zolmitriptan in 0.1NHCl

Zolmitriptan has maximum absorbance at 223nm.The calibration curve of zolmitriptan in 0.1N HCl was plotted by taking concentration range from 1µg/ml to 8µg/ml. The calibration curve for zolmitriptan in 0.1N hydrochloric acid was linear from 1-8 µg/ml with R^2>0.99 (Figure-2.1).

Table-4 Calibration curve of zolmitriptan in 0.1N HCl

Concentration(µg/ml)	1	2	3	4	5	6	7	8
Absorbance	0.13	0.264	0.385	0.495	0.64	0.758	0.877	0.979

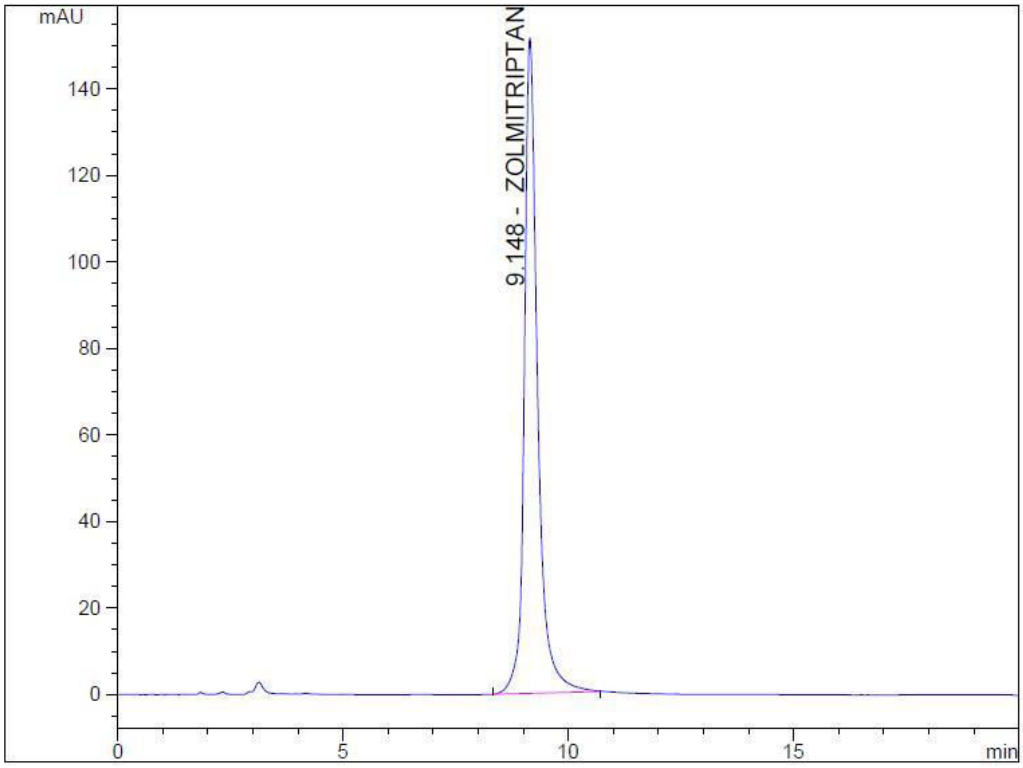
Figure- 1 Calibration curve of zolmitriptan in 0.1N HCl



7.1.2 Calibration curve of zolmitriptan in mixture of buffer (pH 4.0) and acetonitrile (90:10)

The mobile phase has a mixture of buffer and acetronitrile in the ratio of 90:10 which showed a symmetric peak at 9.13 min. The chromatogram was shown in the figure -2.2.

Figure-2 Typical chromatogram of zolmitriptan



A calibration curve was plotted with concentration against peak area as shown in the figure-2.2. The linear regression showed good linearity at a concentration range (n=6) of 25-150µg/ml and the R^2 of > 0.99 was obtained.

Table-5 Calibration curve of zolmitriptan in mixture of buffer and acetronitril e (90%:10%)

Table :5

Conce ntration(µg/ml)	Area
25	663
50	1298
100	2602
125	3275
150	3952

Figure-3 Calibration curve of zolmitriptan in mixture of buffer and acetronitrile (90%:10%)

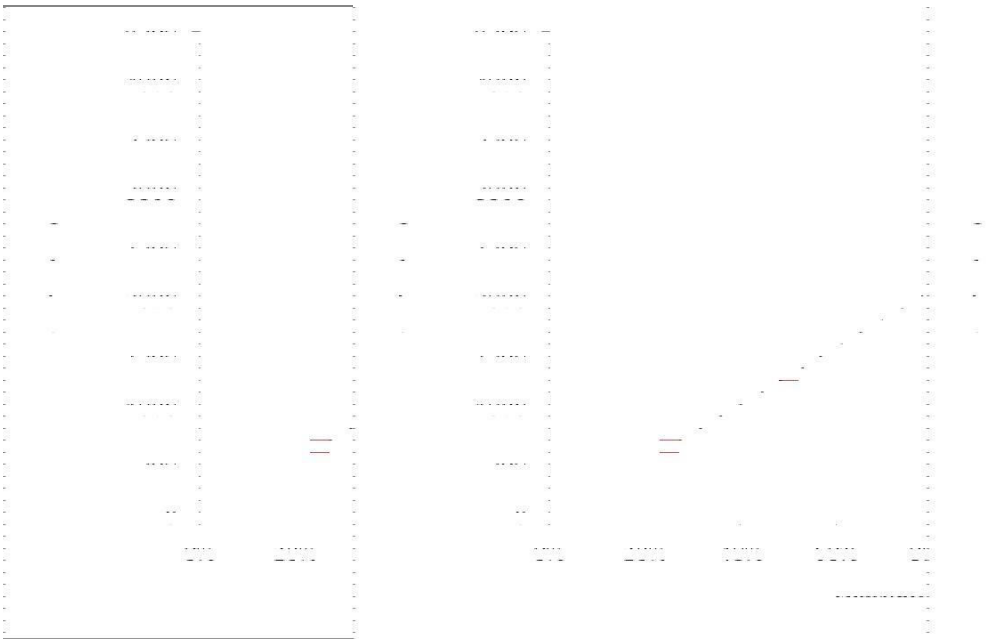


Table-6 Zolmitriptan method validation parameters

Parameter	Value
Retention time(min)	9.15
Linearity	25-150µg/ml
Correlation coefficient(r^2)	0.999
LOD	0.28 µg/ml
LOQ	0.84 µg/ml
Precision intra-day(%RSD)	0.87
Precision inter-day(%RSD)	0.93
Number of theoretical plates	5200
Tailing factor	1.5
Recovery	98%-103%

7.1.3 Evaluation of Zolmitriptan Sublingual Tablets

Evaluation of blend

The Micromeritic properties of the zolmitriptan powder formulations are essential in handling operations because the uniformity of the dose and ease of filling the powder into the container is determined by its flow properties. The powder flow properties can be accessed from Carr's index, Hausner's ratio and Angle of repose. Results for powder formulations were represented in Table-2.7. Results indicate angle of repose $<33^0$ assuring that the flow properties were good for all formulations. Apart from this, Carr's index and Hausner's ratio were <14 and 1.17 respectively for all nine formulations and showed good mixing, flow ability and compressibility.

Table-7: Powder flow properties of the zolmitriptan formulations

Code 1.	Angle of repose(θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Compressibility Index (I)	Hausner's Ratio
F1	32.4±0.1	0.23±0.01	0.26±0.01	11.39±0.25	1.15±0.03
F2	32.00±0.11	0.31±0.01	0.35±0.01	11.54±0.19	1.13±0.00
F3	31.6±0.18	0.22±0.01	0.25±0.01	12.01±0.48	1.13±0.01
F4	31.1±0.17	0.25±0.01	0.29±0.01	13.64±0.27	1.16±0.01
F5	31.3±0.04	0.25±0.01	0.28±0.01	10.86±0.61	1.12±0.00
F6	30.4±0.13	0.25±0.00	0.28±0.01	11.74±1.78	1.13±0.02
F7	30.0±0.13	0.27±0.01	0.30±0.01	10.11±0.20	1.11±0.01
F8	30.4±0.13	0.25±0.00	0.28±0.01	10.84±0.23	1.11±0.02
F9	29.8±0.14	0.26±0.01	0.29±0.01	10.46±0.21	1.12±0.00

All values indicate mean ± standard deviation (SD) n=3

7.1.3.1 Evaluation of prepared zolmitriptan sublingual tablets

The prepared tablets from each formulation are off white, circular, biconcave, odourless which were analysed for thickness, diameter, weight variation, hardness, friability, wetting

time, disintegration time *in vitro*, disintegration time *in vivo*, water absorption ratio, dissolution *in vitro* and uniformity of content (tables-2.8, table-2.9,table-2.10 and table-2.11). The diameter and thickness of all the formulations ranged from 8.03± 0.06 mm to 8.17±0.06 mm and from 3.1±0.0 mm to 3.2±0.0 mm respectively. The average weight of the tablet in all formulations ranged from 150.07 ± 0.06mg to 151.37 ± 0.23 mg. All the tablets formulated in this study met the USP needs for weight variation (USP 31) (Ziya et al., 2011) and in all the formulations it was <2%. The hardness of the tablets was ranged from 4-5kg/cm^2 which indicate good mechanical strength during compression. The friability for all the formulations showed less than 0.5%, demonstrating the friability was within the acceptable limits (USP 31); tablets are not brittle and can handle without difficulty.

The wetting time was measured for all the prepared formulations which were very important parameter in fast disintegrating tablets. It was established to be 66.0±1.0s to 5.0±1.0s which show the highly permeable nature of the tablets. For the optimized formulation (F9) it was found to be 5.0±1.0s which indicates faster disintegration of the tablets. The percentage water absorption for all the formulations was between 154.32±0.01% and 90.75±0.01%.

Table-8 Evaluation tests of sublingual tablets of zolmitriptan

Formulations Code	Diameter(mm) **	Thickness(mm)***	Average weight(mg)***	Hardness (Kg/cm2)**
F1	8.03±0.06	3.17±0.06	151.3 ±0.04	4.33±0.58
F2	8.07±0.06	3.13±0.06	151.37±0.23	4.33±0.58
F3	8.13±0.06	3.17±0.06	151.33±0.58	4.33±0.58
F4	8.13±0.06	3.10±0.06	151.23±0.12	4.66±0.58
F5	8.13±0.06	3.20±0.00	151.13±0.12	4.33±0.29
F6	8.17±0.06	3.17±0.06	151.5±0.10	4.16±0.29
F7	8.13±0.06	3.20±0.00	150.07±0.06	4.16±0.29
F8	8.10±0.00	3.10±0.00	151.17±0.06	4.5±0.50
F9	8.17±0.06	3.17±0.06	151.03±0.06	4.33±0.29

*** **All values show mean ± standard deviation (SD) n=20**

***** All values show mean ± standard deviation (SD) n=6 Table-2.9**

Evaluation tests of sublingual tablets of zolmitriptan

Table : 9

Formulations code	Friability (%) ***	Wetting Time(seconds) *	Water Absorption Ratio (%) *
F1	0.28±0.02	66±1	154.32±0.01
F2	0.18±0.01	55.67±0.58	147.22±0.01
F3	0.13±0.01	43.67±0.58	141.06±0.00
F4	0.24±0.01	15.3±0.58	129.06±0.00
F5	0.30±0.01	14.3±0.58	121.32±0.00
F6	0.33±0.01	12.3±0.58	117.68±0.00
F7	0.29±0.01	10.67±0.58	109.45±0.00
F8	0.33±0.01	6.67±0.58	106.18±0.01
F9	0.30±0.02	5±1	90.75±0.01

***** All values indicate mean ± standard deviation (SD) n=20**

*** All values show mean ± standard deviation (SD) n=3**

The tablets *in vitro* disintegration time is an important parameter which is supposed to be optimized for the improvement of sublingual tablets. The tablet disintegration was effected by

the wicking, swelling nature of the disintegrant (Jinichi et al., 2006). The crospovidone containing tablets speedily wicks the saliva into the tablet which generates an increase in the volume and the hydrostatic pressure provides rapid disintegration in the mouth (Rudnic et al., 1980). Mainly the crospovidone as superdisintegrant uses a blend of swelling and wicking principle. This wicking of liquid into the tablet and particles generated rapid disintegration. Crospovidone swells rapidly in water without getting gel formation due to its high cross link density (Mohanchandran et al., 2011).

All the tablets from each formulation were disintegrated in the range varied from 84.3±0.58s to 7.7±0.58s. From the results formulations containing crospovidone had shown less disintegration time as compared to various superdisintegrants. The reason for delayed disintegration time of sodium starch glycollate and croscarmellose sodium might be due to their tendency to get gel form more when compared with crospovidone. The crospovidone, croscarmellose sodium and sodium starch glycollate were optimized at 6% concentration. After these concentrations of superdisintegrants, there was no much change in the disintegration time.

All the formulations were checked for content uniformity. The uniformity of drug results was good amid various batches of tablets and the % of drug content was greater than 97.5%. The results also indicated acceptable and uniform dispersion of drug in all tablets (table-2.10).

Table-10 Evaluation tests of sublingual tablets of zolmitriptan

Formulations code	*In vitro* disintegration time (seconds)**	Content uniformity (%) ***
F1	84.3 ±0.58	98.06±0.89
F2	57.7±0.58	98.76±1.30
F3	53.7±0.58	99.09±0.19
F4	16.0±1.0	102.9±0.62
F5	15.67±0.58	103.31±0.56
F6	15.0±1	97.66±0.41
F7	11.3±0.58	101.82±0.33
F8	9.3±0.58	101.23±0.41
F9	7.7±0.58	102.23±0.42

*** **All values show mean ± standard deviation (SD) n=20**

** **All values show mean ± standard deviation (SD) n=6**

Table-11 *In vitro* release profile of the zolmitriptan formulations

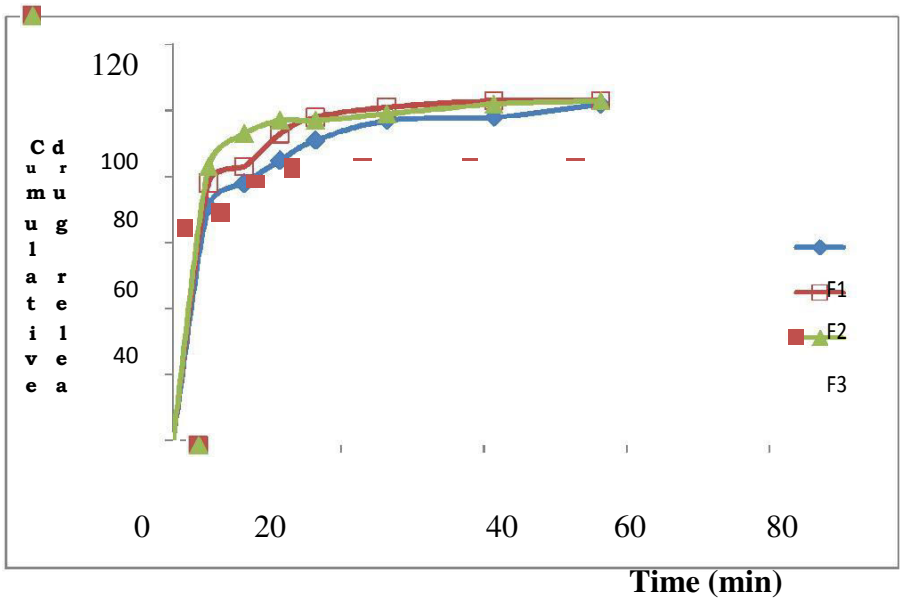
Mins/Formulation code**	F1	F2	F3	F4	F5	F6	F7
5	71.16 ± 2.93	78.83 ± 2.52	83.52 ± 1.01	77.72± 0.73	81.04± 0.81	84.13± 0.46	79.15± 0.78
10	78.17± 3.60	83.29 ± 3.70	93.75± 1.74	84.93± 0.80	84.87± 0.54	95.17± 0.90	86.95± 0.49
15	85.15 ± 2.49	93.32 ± 3.04	97.37 ± 0.69	91.92± 0.82	88.70± 0.27	96.08± 0.54	97.28± 0.59
20	91.90 ± 1.62	98.67 ± 0.64	97.60± 0.20	97.25± 0.81	95.42± 0.75	98.38± 0.29	97.05± 0.95
30	97.47 ± 1.25	101.71 ± 1.41	99.41± 0.64	99.13± 0.72	99.74± 0.92	99.52± 0.66	101.64± 0.99
45	98.68 ± 2.56	103.10 ± 0.40	102.81 ± 0.80	99.13± 0.72	99.74± 0.92	100.91± 0.62	102.09± 0.69
60	102.62 ± 1.75	103.57 ± 0.68	103.50 ± 0.12	101.21± 0.85	102.35± 0.87	102.97± 0.08	103.01± 0.77

****All values indicate mean ± standard deviation (SD) n=6**

7.1.3.2 Comparison of dissolution profile for F1, F2 and F3 zolmitriptan formulations containing 2%, 4% and 6% of sodium starch glycollate.

The *in vitro* dissolution study of formulations F1, F2 and F3 batches showed percentage drug release 85.15 ± 2.49, 93.32 ± 3.04, 97.37 ± 0.69 respectively within 15 minutes. The F3 batch showed good dissolution (figure-2.4) which contained 6% of sodium starch glycollate (table-2.11).

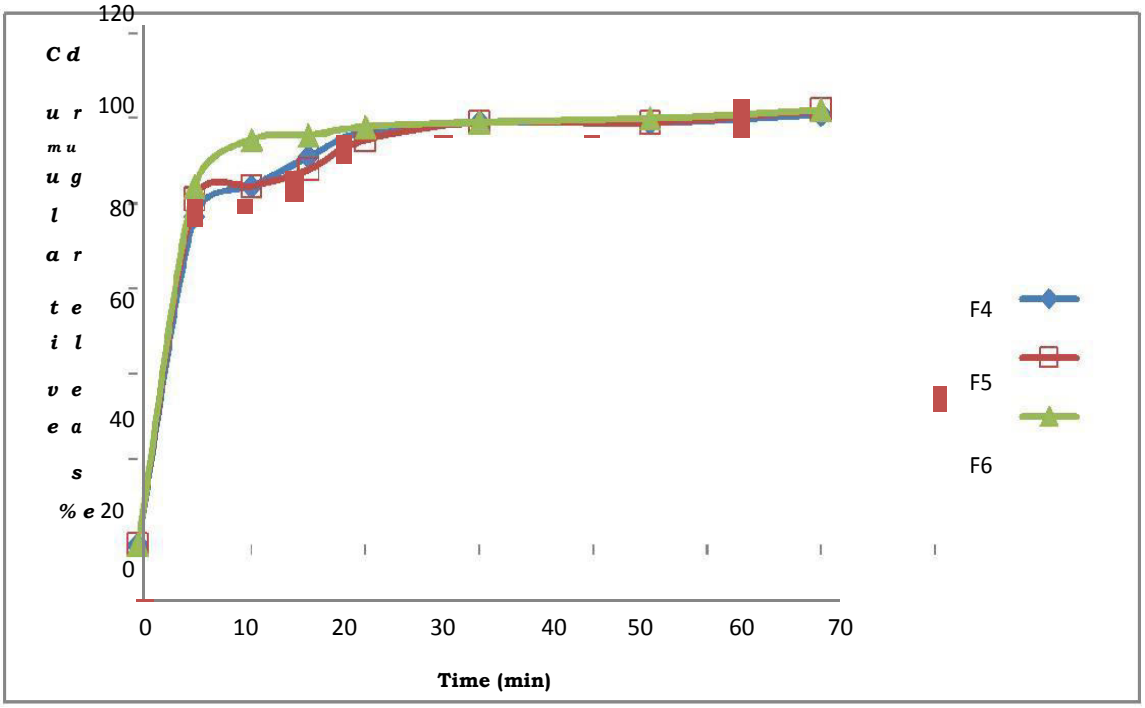
Figure-4 Comparison of dissolution of F1, F2 and F3 zolmitriptan formulations containing 2%, 4% and 6% of sodium starch glycollate.



7.1.3.3 Comparison of dissolution of F4, F5 and F6 zolmitriptan formulations containin2%, 4% and 6% of croscarmellose Sodium.

The *in vitro* dissolution study of formulations F4, F5 and F6 batches showed percentage drug release 91.92±0.82, 88.70±0.27 and 96.08±0.54 respectively within 15 minutes. The F6 batch showed good dissolution (figure-2.5) which contained 6% of croscarmellose sodium (table-2.11).

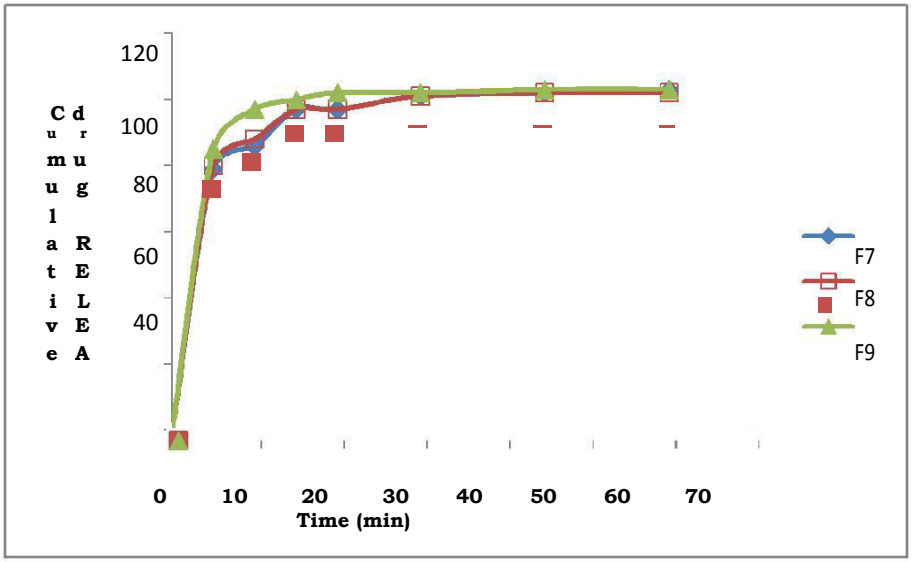
Figure-5 Comparison of dissolution of F4, F5 and F6 zolmitriptan formulations containing 2%, 4% and 6% of croscarmellos sodium.



7.1.3.4 Comparison of dissolution of F7, F8and F9 zolmitriptan formulations containing 2%, 4% and 6% of Crospovidone.

The in-vitro dissolution study of formulations F7, F8 and F9 showed percentage drug release 97.28±0.59, 97.21±0.40 and100.34±1.19 respectively within 15 minutes. The F9 batch showed good dissolution efficiency (100.34±1.19) and less disintegration time compared with all formulations (figure-2.6) which contains 6% of crospovidone (table-2.11). This formulation (F9) was selected as optimised and subjected for characterisation.

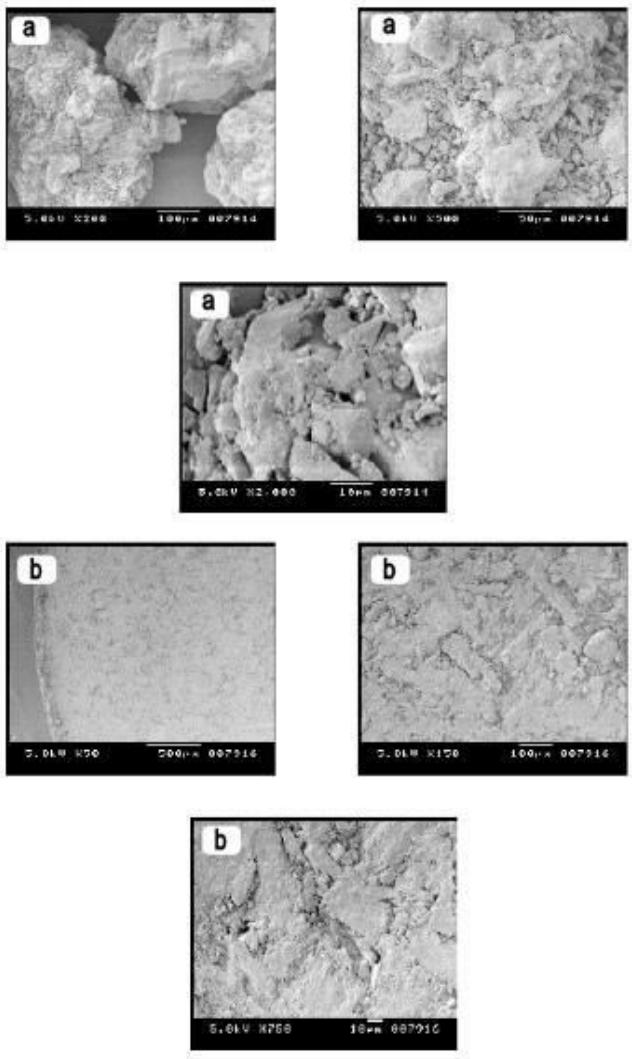
Figure-6 Comparison of dissolution of F7, F8 and F9 zolmitriptan formulations containing 2%, 4% and 6% of crospovidone.



7.1.4. Scanning Electron Microscopy (SEM) studies

Surface morphology of sublingual zolmitriptan formulation and Standard zolmitriptan were examined by scanning electron microscopy (Figure-2.7). The SEM micrographs reveal that there is no segregation or deposition of particles on the surface of sublingual tablets (Alhusban et al., 2010).

Figure-7 Scanning Electron Microscope images of a) zolmitriptan standard b) zolmitriptan sublingual tablets.



7.1.5. Evaluation of stability studies

The optimized form ulation (F9) were subjected for stability studies by keeping the formulation a t 40±2^0 C/75±5% RH and analyzed for every month for three months. Drug content, hardness, friability, wetti ng time and disintegration time *in vitro* were evaluated. The optimized for mulations are stable and did not show much variation in any of the paramet ers (Sunita et al., 2010).

Table-12 Effect of storage of formulation F9 at 40±2^0 C/75±5% RH

Code/day F9	Drug content (%) **	Hardness (kg/cm^2) **	Friability (%) ***	Wetting time (min) *	*In vitro* disintegration (min) **
1St day	102.23±0.42	4.33±0.29	0.30±0.02	5.00±1.00	7.7±0.58
30Th day	101.91±0.01	4.33±0.58	0.30±0.01	5.33±0.58	7.67±0.58
60Th day	101.9±0.01	4.16±0.29	0.33±0.01	5.33±0.58	8.0±0.0
90Th day	101.87±0.01	4.66±0.58	0.33±0.01	5.33±0.586	8.0±0.0

*** **All values show mean ± standard deviation (SD) n=20**

** **All values show mean ± standard deviation (SD) n=6**

* **All values show mean ± standard deviation (SD) n=3**

8.0 CONCLUSION

Fast dissolving zolmitriptan sublingual tablet was prepared with the help of direct compression technique by using sodium starch glycollate, croscarmellose sodium and crospovidone as superdisintegrants. The formulae was optimized for zolmitriptan sublingual tablet to give fast relief and increase the patient compliance. The unpleasant taste of these drug was masked by aspartame (sweetener). The tablet containing 6% of crospovidone showed faster disintegration and more dissolution efficiency. The characterisation of optimised formulation was done and the result showed without any interaction among the drug and excipients. Optimized formulation was subjected to stability studies and studies confirmed that the tablet was stable. These optimised formulation was evaluated for *in vivo* release studies using rabbit model and showed effective therapeutic Cmax when compared to clinical dose. The study concludes that these formulated fast disintegrating sublingual tablet is promising alternative to oral administration route in acute management of migraine.

9.0 SUMMARY

In the present study fast disintegrating sublingual tablets of potent anti-migraine drug of zolmitriptan (5mg/tablet) and was prepared by the help of direct compression technique. The superdisintegrants used were sodium starch glycollate, croscarmellose sodium and crospovidone. Mannitol and avicel pH102 (microcrystalline cellulose) were used as diluents. Aspartame was used as a sweetener and magnesium stearate was selected as a lubricant.

The blend of all powder formulation was examined for angle of repose, Carr's Compressibility Index and Hausner's Ratio. Results showed that the angle of repose is <33° assuming good flow properties for formulation. Carr's compressibility index and Hausner's ratio were found to be <14 and <1.17 for zolmitriptan powder formulation respectively, ensuring that all the preparation resulted in good mixing, flow ability and compressible characteristics. The formulated tablet was evaluated for physiochemical properties and dissolution efficiency. Good drug uniformity results were established among different batches of tablet and it was more than 97.5% ($p<0.05$) in zolmitriptan.

The wetting time and disintegration time for zolmitriptan sublingual tablet was found to be 66.0±1.0s to 5.0±1.0s and 84.3±0.58s to 7.7±0.58s respectively. The tablet containing 6% crospovidone showed faster disintegration and more dissolution efficiency. The tablet disintegration was effected by the wicking and swelling nature of the disintegrants. The crospovidone present in the tablets is responsible for the quick wicks of saliva into the tablet and volume expansion is generated and hydrostatic pressure, which provides quick disintegration in the mouth (Jinichi et al., 2006). Based on faster disintegration and dissolution efficiency the formulation nine (F9) was selected as optimised. The wetting and disintegration time for

optimised formulation (F9) was found to be 5±1s and 7.7±0.58s for zolmitriptan tablet. The optimised formulation showed 100.34±1.19 dissolution efficiency for zolmitriptan sublingual tablet.

The optimized formulation was characterized with the help of Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR); in this formulation the SEM pictures reveal that there was no segregation or deposition of particles on the surface of sublingual tablet. From DSC and PXRD studies, it was observed that in this optimised formulation the drug exists in crystalline form without having polymorphic change. FTIR studies revealed that the drug and excipients did not have interactions. Based on disintegration and dissolution studies, the optimized preparations were subjected to stability studies. These formulation was analysed for drug content, friability, hardness, wetting time and *in vitro* disintegration time for three months. The optimised formulation was stable and did not show much variation in any of the parameters.

Comparative pharmacokinetic studies of prepared zolmitriptan tablet (5mg/tablet) and intravenous injection (5mg/kg) were carried out using New Zealand rabbits. The Cmax, T1/2, Tmax and AUC were calculated.

Peak serum concentration attained by the test item zolmitriptan was 140.622ng/ml and 2500.846ng/ml following sublingual and intravenous administration respectively. The time needed to attain peak serum concentration by drug, following sublingual and intravenous administration was 1 hr and 0.083 hr respectively. The area under the curve AUC(0 – 24), was found to be 231.769 ng.hr/ml and 1712.739 ng.hr/ml for sublingual and intravenous

administration respectively. AUC(0 - ∞) was calculated and was found to be 295.131ng.hr/ml and 1750.454ng.hr/ml for sublingual and intravenous administration respectively. The T1/2 was found to be 0.855 hr and 1.665 hr following sublingual and intravenous administration respectively.

Intra venous route gives 100% bioavailability where as oral or sublingual gives less bioavailability due to absorption, first-pass effect, receptor binding, rapid absorption etc. In the present market zolmitriptan oral and nasal formulations are available and the oral bioavailability of zolmitriptan is 25% (10mg/kg rabbit) suggesting significant first metabolism in rabbit. So sublingual route of administration helps the bioavailability and the maximum concentrations attained with zolmitriptan at 5mg tablet in rabbits elicits the pharmacological activity. The main object of this study is to show fast absorption of the drug and provide more consistent relief from migraine.

In conclusion, the average plasma concentration-time profiles for zolmitriptan 5 mg tablet by sublingual route show quite rapid initial drug absorption, on normal reaching 80% of eventual Cmax within 1 hour and 5 mg/kg intravenous route show time to peak plasma concentration within 1 hour. Zolmitriptan 5 mg tablet by sublingual route in rabbits showed effective therapeutic Cmax (140.622 ng/ml) when compared to clinical dose by oral route (5.6 ng/ml).

10.0 BIBLIOGRAPHY

1. Alessandro P, Elisabetta DZ, Alessia G, Irene V, Paolo C, Giorgio DV and Alessandro P. The migraine-ichemic stroke relation in young adults. Stroke research and treatment, Article id 304921, 2011, Doi 10.406/2011/304921.

2. Alhusban F, Perrie Y and Mohammed AR. Formulation and characterisation of lyophilised rapid disintegrating tablet using amino acids as matrix forming agents. European Journal of Pharmaceutics and Biopharm, 75, 2010, 254-262.

3. Allen LV and Wang B. Method of making a rapidly dissolving tablet. US patent 5,635,210, 1997.

4. Allen LV and Wang B. Process for masking a particulate support matrix for making rapid dissolving tablet. US patent 5,587,180, 1996.

5. Allen LV. Rapid-dissolve technology: An interview with Lloyd. Allen. IJPC, 7(6), 2003, 449–450.

6. Amin AF, Shaah TJ, Bhadani MN and Patel MM. Emerging trends in orally disintegrating tablets. www.pharminfo.net, 2005.

7. Andries F, Marais, Mingna Song, Melgardt, M and Villers De. Effect of compression force humidity and disintegrants and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant. Tropical Journal of Pharmaceutical Research, 2, 2003, 125-135.

8. Anupama K, Shellyn K, Neena B. Formulation and evaluation of mouth dissolving tablets of Oxcarbazepine. International journal of Pharmacy and Pharmaceutical sciences, 1(1), 2009, 12-23.

9. Arjun G, Sravan Prasad M, Santhosha D and Achaiah G. Formulation and evaluation of rosiglitazone mouth dissolving tablet. International Journal of Pharma and Bio Sciences, 5(1), 2010, 1-9.

10. Asad R, Tariq M A and Shahida BN. A novel Spectrophotometric method for the determination of zolmitriptan in pharmaceutical formulations. Journal of the Chinese Chemical Society, 54, 2007, 1413-1417.

11. Avani FA. Emerging trends in the development of orally disintegrating tablet technology. Latest reviews, 4(1), 2006.

12. Azza A, Mahmoud and Salwa S. Fast relief from migraine attacks using fast-disintegrating sublingual tablets. Drug Development and Industrial Pharmacy, 2011, 1-8.

13. Bhaskaran S and Narmada GV. Indian Pharmacist, 1(2), 2002, 9-12.

14. Bhaskaran S and Narmada GV. Rapid Dissolving tablet A Novel dosage form Indian Pharmacist, 1, 2002, 9-12.

15. Biradar SS, Bhagavati ST and kuppasad IJ. Fast dissolving drug delivery systems: a brief overview. The Internet Journal of Pharmacology, 4(2), 2006,

16. Birudaraj R, Berner B and Shen S. Buccal permeation of buspirone: mechanistic studies on transport pathways. Journal of Pharmaceutical Sciences, 94, 2005, 70-78.

17. Botha SA, Lötter AP and Du Preez JL. DSC screening for drug–excipient and excipient–excipient interactions in poly pharmaceuticals intended for the alleviation of the symptoms of colds and flu III. *Drug Development and Industrial Pharmarmcy,* 13(7), 1987, 1197–1215.

18. Chang RK, Guo X, Burnside A and Couch RA. Fast dissolving tablets. The journal of Pharmacy Technology*, 6,* 2000, 52–58.

19. Cheng H, Polvino WJ and Sciberras D. Pharmacokinetics and food interactions of MK-462 in healthy males. Biopharm Drug Disposition, 17, 1996. 17-24.

20. Cooper CB, Bai TR, Heyderman E and Corrin B. Cellulose granulomas in the lungs of a cocaine sniffer. *Br Med J,* 286, 1983, 2021–2022.

21. Corveleyn S and Remon JP. Formulation and production of Rapidly Disintegrating Tablets by Lyophilization using Hydrochlorthiazide as a model drug. International Journal of Pharmaceutics, 152, 1997, 215-225.

22. Dahl TC, Sue IT and Yum A. The influence of disintegrant level and capsule size on dissolution of hard gelatin capsules stored in high humidity conditions. *Drug Development and Industrial Pharmacy,* 17(7), 1991, 1001–1016.

23. Dail MM, Moench PA, Mathias NR, Stetsko PL, Heram CL and Smith RL. A rabbit model for sublingual drug delivery: comparison with human pharmacokinetic studies

of propranolol verapamil and captopril. Journal of Pharmaceutical Sciences, 95, 2006, 34-44.

24. Debjit B, Chiranjib B, Krishnakanth, Pankaj R and Margret C. Fast dissolving tablets: an overview. Journal of Chemical and Pharmaceutical Research, 1(1), 2009, 163-177.

25. Debord B, Lefebvre C, Guyot Hermann AM, Boucher and Guyot JC. Study of

26. Different crystalline forms of mannitol comparative behaviour under compression

27. Drug Dev Ind Pharm, 13, 1987, 1533-1546

28. Evarajan PV and Gore SP. Express Pharma Pulse, 11(23), 2000, 16. Dowson AJ, Shapero G, Baos V and Smith R. Primary care needs assessment for guidance on Headache management. Headache Care, 2, 2005, 43-46.

29. Elina T, Janne M, Riikka L, Joakim R, Tonmi J, Jarkko K, Kristiina J and Pekka J. Fast-dissolving sublingual solid dispersion and cyclodextrin complex increase the absorption of perphenazine in rabbits. Journal of Pharmacy and Pharmacology, 63, 2011, 19-25.

30. Emma J, Seaber, Richard W, Peck, Deborah, A and Smith JA. The absolute bioavailability and effect of food on the pharmacokinetics of Zolmitriptan in healthy volunteers, British Journal of Clinical Pharmacology, 46, 1998, 433-439.

31. Fu Y, Yang S, Jeong SH, Kimura S and Park K. Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. Critical Review in Therapeutic Drug Carrier Systems, 21(6), 2004, 433–476.

32. Gohel M C. A review of co–processed directly compressible excipients. Journal of pharmacy and Pharmaceutical Sciences, 8(1), 2005, 76-93.

33. Gohel M, Patel M, Amin A, Agrawal R, Dave R and Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vaccum drying technique. AAPS PharmSciTech, 5(E36), 2004.

34. Gohel MC. A review of co –processed directly compressible excipients. Journal of pharmacy and Pharmaceutical Sciences, 8(1), 2005, 76-93.

35. Gole DJ. US Patent 5215756, 1993.

36. Gordon MS and Chowhan ZT. The effect of aging on disintegrant efficiency in direct compression tablets with varied solubility and hygroscopicity, in terms of dissolution. *Drug Development and Industrial Pharmacy, 16,* 1990, 437–447.

37. Gordon MS, Rudraraju VS, Dani K and Chowhan ZT. Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets. *Journal of Pharmaceutical Sciences,* 82(2), 1993, 220–226.

38. Goswami T and Jasti XLi. Sublingual drug delivery. Critical Review in Therapeutic Drug Carrier Systems, 25, 2008, 449-484.

39. GU X, Simons FER and Simons KJ. Epinephrine absorption after different routes of administration in an animal model. Biopharm Drug Disposition, 20, 1999, 401-405.

40. Habib W, Khankari RK and Hontz J. Fast-dissolve drug delivery systems. Critical Review in Therapeutic Drug Carrier Systems, 17, 2000, 61-72.

41. Hedlund C, Rapoport AM, Dodick DW and Goadsby PJ. Zolmitriptan nasal spray in the acute treatment of cluster headache: a meta-analysis of two studies. Headache, 49, 2009, 1315-1323.

42. Heinemann H and Rother W. US patent 3885026, 1998.

43. Hipasawa N, Ishise S, Miyata M and Danjo K. Application of nilvadipine solid dispersion to tablet formulation and manufacturing using crospovidone and methylcellulose on dispersion carriers. *Chem Pharm Bull,* 52(2), 2004, 244–247.

44. Hisakadzu B and Yunxia. Preparation evaluation and optimization of rapidly disintegrating tablets, Powder Technology, 122, 2002, 188–198.

45. Honda Y and Nakano M. Evaluation of preference for swallowing orally disintegrating famotidine tablet in outpatients. Japan Journal of Hospital Pharmacy, 24, 1998, 533–540.

46. Honey G, NISHANT V AND Vikas R. A novel approach to optimize and formulate fast disintegrating tablets for nausea and vomiting. American Association of Pharmaceutical Scientists, 9(3), 2008, 774-781.

47. Hu XH, Markson LK, Lipton Rb, Stewart WF and Berger ML. Burden of migraine in the United States: Disability and economic costs. Archives of Internal Medicine, 159, 1999, 813-818.

48. Indurwade NH, Rajyaguru TH and Nakhat PD. Indian Drugs, 39(8), 2002, 405-409.

49. Ishikawa T, Kuizumi N, Mukai B, Utoguchi N, Fujii M, Matsumoto M, Endo H, Shirrotake S and Watanabe Y. Preparation of rapidly disintegrating tablet using new

types of microcrystalline cellulose (PH-M series) and L-HPC by direct compression method. Chem Pharm Bull, 49, 2001, 134-139.

50. Jaccard TT and Leyder J. Une Nouvelle forme galenique: Le Lyoc. Ann Pharm Fr, 43(2), 1985, 123-131.

51. Jarosz PJ and Parrott EL. Effect of tablet lubricants on axial and radial work of failure. Drug Development and Industrial Pharmacy, 8, 1982, 445-453.

52. Jinichi F, Etsuo Y, Yasuo Y, Katsuhide T. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. International Journal of Pharmaceutics, 310, 2006, 101-109.

53. Joachim J, Kalantzis G and Delonca H. The compression of effervescent aspartame tablets: the influence of particle size on the strain applied on the punches during compression. *J Pharm Belg,* 42, 1987, 17–28.

54. Ketan A, Mehta, Serpil KM, Wantanee P, Waseem MA, Navnit H and

55. Shah. Multi-unit controlled release system of nifedipine and nifedipine: pluronic F-68 solid dispersion: Characterization of release mechanisms, Drug Development and Industrial Pharmacy, 28(3), 2002, 275-285.

56. Kilic B, Ozden T, Toptan S and Ozilhan S. Simultaneous LC-MS-MS determination of zolmitriptan and its active metabolite N-desmethyl zolmitriptan in human plasma. Chromatographia supplement, 66, 2007, S129-S133. Koizumi, Watanabey, Moritak and Utoguchin, Matsumoto M. New method of preparing high porosity rapidly saliva soluble

compressed tablet using mannitol with camphor. A sublining material. International Journal of Pharmaceutics, 152, 1997, 127-31.

57. Kuccherkar BS, Badhan AC and Mahajan HS. Mouth dissolving tablets: A novel drug delivery system, Pharma Times, 35, 2003, 3-10.

58. Kumar S, Sachdeva M and Bajpai M. Formulation and Evaluation of Mouth Dissolving Tablets Sildenafil Citrate, Journal of Pharmaceutical Science and Technology, 2(4), 2010, 202-206.

59. Kurosaki T, Takatori T, Nishimura H, Nakayama T and Kimura T. Regional variation in oral mucosal drug absorption permeability and degree of keratinisation in hamster oral cavity. Pharmaceutical Research, 1991.

60. Lachman L and Liberman HA. Theory and practice of Industrial pharmacy. 3rd edition, 293-294.

61. Laitinen R, Suihko E, Toukola K, Bjorkqvist M, Riikonen J, Lehto, VP, Jarvinen K and Ketolainen J. Intraorally fast-dissolving particals of a poorly soluble drug: preparation and in vitro characterisation. European Journal of Pharmaceutics and Biopharmaceutics, 71, 2009, 271-281.

62. Launer LJ, Terwindt MG and Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology, 53(3), 1999, 537-542.

63. Leow K, Smith M, Watt J, Williams B and Cramond T. Comparitive oxycodone pharmacokinetics in humans after intravenous, oral and rectal administration. Therapeutic Drug Monitoring, 14, 1992, 479-484.

64. Lipton RB, Stewart WF, Eady R, Hall CO, Quinn S, Kuhn T and Gutterman D. Sumatriptan for range of Headaches in migraine suffer: results of spectrum study. Headache, 40, 2004, 783-791.

65. Malkaw AH, Al-Ghannaneem AM and Crooks P A. Development of a GC-MS assay for the determination of Fentanyl Pharmacokinetics in rabbit plasma after sublingual spray delivery. The AAPS Journal, 10(2), 2008, 261-267.

66. Mannila J, Tomi J, Kristiina J, Maarit ME, Bigal, Carlos A, Bordini AL.

67. Antoniazz[I], José G and Speciali, Triptan the formulations. A critical evaluation. Arq. Neuro-Psiquiatr, 61(2A), 2003.

68. Marcelo E, Bigal, Carlos A and Bordini AL, Antoniazz[I]JG, Speciali triptan the formulations. A critical evaluation. Arq. Neuro- Psiquiatr, 61(2A), 2003.

69. Martin GR. Inhibition of the trigemino-vascular system with 5-HT1D drugs: selectively targeting additional sites of action, (2), 1996, 13-18.

70. Martin GR. Pre-clinical pharmacology of Zolmitriptan (zomig; formerly 311C90: a centrally and peripherally acting 5HT1B/1D agonist for migraine. Cephalalgia, 17(18), 1997, 4-14.

71. Matsubara Y, Kawjiri A and Ishiguro F. Granules with suppressed Bitterness. JP 02.056,416, February 26.1990.

72. Misra TK, Currington JW, Kamath SV, Sanghvi PP, Sisak JR and Raiden MG. US patent 5869098, 1999.

73. Mohanachandran PS, Sindhumol PG and Kiran TS. Superdisintegrants: an overview. International Journal of Pharmaceutical Sciences Review and Research, 6(1), 2011, 105-109.

74. Mutasem M, Rawas Q, Estelle F, Simons R, MD, Keith J and Simons. Sublingual epinephrine tablets versus intramuscular injection of epinephrine: dose equivalence for potential treatment of anaphylaxis. Journal of allergy and clinical Immunology, 117(2), 2006, 398-403.

75. Mutasem M, Rawas Q, F. Estelle R. Simons, Keith J and Simons. Fast disintegrating sublingual tablets: effects of epinephrine load on tablet characteristics. American Association of Pharmaceutical Scientists PharmSciTech, 7(2), 2006, E1-E7.

76. Nanda A, Kandarapu R and Garg S. An update on taste masking technologies for oral pharmaceuticals. Indian J Pharm Sci, 64, 2002, 10-17.

77. Oduu P, Barthelemy C, ChatelierD, Luyckx M, Brunt C, Dine T, Gressier B, Cazin M, Cazin JC and Robert H. Pharmacokinetics of midazolam: Comparison of sublingual and intravenous routes in rabbit.

78. European Journal of drug metabolism and Pharmacokinetics, 24, 1999,1-7.

79. Omray A and Omray P. Evaluation of microcrystalline cellulose as a glidant. *ndian Journal of Pharmaceutical Sciences, 48,* 1986, 20–22. Parul M S, Patel B, Amit choudhary and Gupta GD. Fast dissolving drug delivery systems. 2006, an update.

80. Pebley WS, Jager NE and Thompson SJ. Rapidly disintegrating tablets, US patent 5,298,261, 1995.

81. Pilpel N. Metal stearate in pharmaceuticals and cosmetics. Manuf Chem Aerosol News, 42(10), 1971, 37-40.

82. Prajapati BG and Nayan RA. A review on recent patents on fast dissolving drug delivery system. International journal of Pharm Tech Research, 1(3), 2009, 790-798.

83. Prashant K, Kavita R, Gajbhiye, Vikas DV, Rajesh SJ, Sachin M, Amit S, Mohit B, Sanjay KS and Sanjay G. Preparation and evaluation of mouth dissolving tablets of meloxicam. International Journal of Drug Delivery, 2, 2010, 76-80.

84. Rahul C, Zahra H, Farhan A, Alan M, Smith, Afzal R and Mohammad. The role of formulation excipients in the development of lyophilised fast disintegrating tablets. European journal of Pharmaceutics and Biopharmaceutics, 72, 2009, 119-129.

85. Rameshwari S and Jeya AJ. Formulation and evaluation of nifedipine sublingual tablets. Asian Journal of Pharmaceutical and Clinical Research, 2(3), 2009, 44-48.

86. Rapoport AM, Bigal ME, Tepper SJ and Sheftell FD. Zolmitriptan (Zomig^{R}). Expert Rev Neurotherapeutics, 4, 2004, 33-41.

87. Renon JP and Corveleyn S. Freeze-dried rapidly disintegrating tablets. US patent 6,010,719, 2000.

88. Rudnic EM, Lausier JM, Chilamkarti RN and Rhodes CT. Studies on the utility of cros-linked polyvinylpyrrolidone as a tablet disintegrant. Ind Pharm, 6, 1980, 291-309.

89. Sameer G, Late, Yi-Ying Yu, Ajay K and Banga. Effect of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. International Journal of Pharmaceutics, 365, 2009, 4-11.

90. Schiermeier SPC and Schmidt. Fast dispersible ibuprofen tablets. European Journal of Pharmaceutical Sciences, 15, 2002, 295–305.

91. Seager H. Drug delivery products and Zydus fast dissolving dosage forms, Journal Pharm Pharmacology, 50, 1998, 375-382.

92. Setty CM, Prasad DVK, Gupta VRM and BSa. Development of fast dispersible aceclofenac tablets: effect of functionality of superdisintegrants. Indian Journal of Pharmaceutical Sciences, 70(2), 2008, 180-185.

93. Shailesh S, Rajeev G, Naruka PS and Gupta GD. Fast dissolving tablet: The future of compaction, Latest reviews, 5(2), 2007.

94. Shangraw RF. Compressed tablets by direct compression. In: H. A. Lieberman L Lachm. Pharmaceutical dosage Forms, Tablets Vol I, Marcel Dekker, New York, 1989, 195-246.

95. Shapero G, Dowson A, Lacoste JP and Almqvist P. Improved migraine management in primary care: results of a patient treatment experience study using zolmitriptan orally

disintegrating tablet. International Journal of Clinical Practice, 60(12), 2006, 1530-1535.

96. Sharma S, Singh G and Gupta GD. Formulation design and optimization of mouth dissolving tablets of domperidone using sublimation technique. Pharma science Monitor, 1(1), 2010, 128-136.

97. Sharma S, Singh G and Gupta GD. Formulation design and optimization of mouth dissolving tablets of domperidone using sublimation technique. Pharma Science Monitor, 1(1), 2010, 128-136.

98. Shen RW. Taste Masking of Ibuprofen by Fluid Bed Coating. US patent 5,552,152, 1996.

99. Stovner LJ, Zwart K, Hagen K, Terwindt GM and Pascual J. Epiderminology of headache in Europe, European journal of Neurology, 13(4), 2006, 333-345Suzuki K. Rheological study of vanishing cream. Cosmet toilet, 91(6), 1976, 23-31.

100. Takao M, Tetsuya T, Hitohi K, Atsushi K, Shigeru I. Formulation design of taste-masked particles, including famotidine, for an oral fast-disintegrating dosage form. Chem Pharm Bull, 56(4), 2008, 530-535.

101. Takao M, Yoshinori M, Takeshi Y, Estuo Y and Katsuhide T. Formulation design of a novel fast-disintegrating tablet. International Journal of Pharmaceutics, 306, 2005, 83-90.

102. Takuma K, Hiraku O, Yuri T, Minoru U and Yoshiharu M. Development of novel fast-disintegrating tablets by direct compression using sucrose stearic acid ester as a

disintegration-accelerating agent. Chem Pharm bull, 56 (10), 2008, 1384-1388.

103. Tarvainen and Pekka J. Effects of RM-β-CD on sublingual bioavailability of 9-tetrahydrocannabinol in rabbits. European journal of Pharmaceutical Sciences, 26, 2005, 71-77.

104. Toshihiro S, Masae S, Yoshiniro N, Daisuke I, Yoshio M, Kazuhiro O, Tetsuro T, Naoru H and Yasutaka I. Formulation study for lansoprazole fast disintegrating tablet III. Design of rapidly disintegrating tablets. Chem Pharm Bull, 51(10), 2003, 1121-1127.

105. USP/NF. Physical Tests: Disintegration. Rockville MD, United states Pharmacopeial convention Inc, 21/17edition, 2003, 701.

106. USP/NF. Physical tests: Disintegration. Rockville MD, United states Pharmacopeial convention Inc, 21/17 edition, 2003, 701.

107. USP/NF. Physical tests: Tablet friability. Rockville MD, United states pharmacopeial convention Inc, 26/21 edition, 2003, 1216.

108. USP/NF. Physical tests: Uniformity of dosage Units. Rockville MD, United states Pharmacopeial convention Inc, 26/21 Edition , 2003, 905.

109. Vijayakumar EKS, Samel MA, Bhalekar SB and Pakhale SM. A new stability indicating HPLC method for related substances in zolmitriptan. Indian Journal of Pharmaceutical Sciences, 2010, 119-122.

110. Wallace JW, Capozzi JT and Shangraw RF. Performance of pharmaceutical filler/binders as related to methods of powder characterization. *Pharmaceutical Technology,* 7(9), 1983, 94–104.

111. Watanabe Y, Koizumi K, Zama Y, Koriyama M, Matsumoto Y and Matsumoto M. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrates. Biol Pharm Bull ,18, 1995, 1308-1310.

112. Wertz PW, Hoogstraate AJ and Squier CA. Biochemical basis of the permeability barrier in skin and oral mucosa. Hamilton, New York: Marcel Dekker, Inc, 1996.

113. Yara P, Armando, Simon GS, Marina de FS, Eunice KK, Eunice E M K, Valentina P and Cristina H dos RS. Bioequivalence assay between orally disintegrating and conventional tablet formulations in healthy volunteers. International Journal of Pharmaceutics, 366, 2009, 149-153.

114. Yarwood RJ, Kearny K and Thomson AR. Process for preparing solid dosage form for unpalatable pharmaceuticals. US patent 5,738,875, 1998.